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ABSTRACTS OF WORLD MEDICINE

It is the aim of this journal to provide the reader with abstracts of all important articles appearing in medical periodicals published in every part of the world, and in this way to enable him to keep in touch with new developments throughout the whole field of medicine and in each of its special branches, including those aspects of surgery which are of particular concern to the physician.

More than 1,600 periodicals are surveyed, from which are selected for abstracting those papers which appear to make some useful contribution to the sum of medical knowledge or experience. Each paper is abstracted in sufficient detail to indicate to the general reader the nature and value of that contribution and to enable the specialist to assess its importance in relation to his own work and to decide whether the original article should be read in full. The author's own summary or an editorial summary published with the original article may occasionally be reproduced if it is suitable for these purposes, and the title and reference alone may be published in order to draw attention to a review article or other type of paper which cannot readily be abstracted.

The abstracts in each issue are grouped in sections according to subject and, so far as possible, those dealing with medical and surgical aspects of the same problem appear together. The titles of papers written in languages other than English are given both in translation and in the original form. The titles of journals are given in full and also abbreviated according to the rules adopted in the *World List of Scientific Periodicals*, as modified by *ISO Recommendation R4: International Code for the Abbreviation of Titles of Periodicals* (International Standards Organization, 1957), and in *World Medical Periodicals* (Second Edition, World Medical Association, 1957). The transliteration of authors' names from the Cyrillic alphabets is in accordance with *ISO Recommendation R9: International System for the Transliteration of Cyrillic Characters* (International Standards Organization, 1955).

Explanatory or critical comments by the abstracter or editor are enclosed within square brackets.

ABSTRACTS OF WORLD MEDICINE

VOL. 30 NO. 4 OCTOBER, 1961

Pathology

831. **The Site of Leucocyte Emigration during Inflammation**

V. T. MARCHESI. *Quarterly Journal of Experimental Physiology and Cognate Medical Sciences* [*Quart. J. exp. Physiol.*] **46**, 115–118, April, 1961. 22 figs., 10 refs.

An investigation was carried out at the Sir William Dunn School of Pathology, Oxford, to determine whether leucocytes emigrate from venules by way of the intercellular junctions or through the cytoplasm. The mesentery of rats was subjected to mechanical trauma and 2 hours later pieces were removed, fixed in 1% phosphotungstic acid, and sections prepared for examination under the electron microscope.

In a number of excellent plates the appearances are reproduced in the form of serial views. A leucocyte, which sticks to the wall of the venule, is seen to extend a pseudopod into the wall in such a way that the endothelial intercellular junction is dissected apart. Serial photomicrographs show the same leucocyte progressing on its journey through the endothelial wall. Neutrophil and eosinophil granulocytes and monocytes were found to behave in this way. No specialized features, such as holes or channels, were discovered in the endothelium.

G. Loewi

832. **Experimental Avitaminosis-E as a Mode of Progressive Muscular Dystrophy in Man.** (Экспериментальный Е-авитаминоз как модель прогрессивной мышечной дистрофии человека)

M. G. ŠČERBAKOVA. *Архив Патологии* [*Arh. Patol.*] 23, 15–23, No. 4, 1961. 6 figs., bibliography.

The author presents a detailed and illustrated account of the histopathology of muscle in rabbits maintained on a diet devoid of vitamin E until their death, which occurred within 15 to 34 days, the series consisting of 45 experimental and 14 control animals. The histological picture was found to be similar to that of progressive muscular dystrophy in man. The essential degenerative process is called a " de-differentiating dystrophy "; this is characteristically patchy, giving a mosaic appearance, and consists in waxy degeneration of the muscle fibres, with homogenization but no contractures. *A. Swan*

833. **Levels of Blood-coagulation Factors during Anticoagulant Therapy with Phenindione**

K. W. DENSON. *British Medical Journal* [*Brit. med. J.*] 1, 1205–1210, April 29, 1961. 4 figs., 25 refs.

The author reports from St. Pancras Hospital (University College), London, the results of an investigation into the levels of specific blood coagulation factors determined frequently in 6 patients with coronary thrombosis undergoing a course of anticoagulant therapy with phenindione (" dindevan "; 2-phenyl-1:3-indanedione) and at random times in a further 19 patients receiving long-term or short-term anticoagulant therapy. The methods for each factor are described.

Reduction in the concentration of Factor VII, the Prower–Stuart factor, Christmas factor, and total thromboplastic factors correlated well with the values for the one-stage prothrombin time when stable values for the latter had been obtained. Thus with stabilization within the therapeutic range there should be no predisposition to haemorrhage. It was noted that the level of Factor VII rose and fell precipitously in response to changes in dosage and, whereas the decrease in Factor VII was the earliest indication of a decrease in other factors, the equally rapid increase in this factor often masked the continued reduction in the levels of other factors. The value for Christmas factor was reduced early in therapy probably because of the initial administration of heparin in association with phenindione; it tended to rise, however, when heparin was discontinued and thereafter paralleled very closely the values for the Prower–Stuart factor and total serum thromboplastin factors, but always at a higher level. The concentration of prothrombin, as measured by the two-stage technique, showed relatively little response to changes in dosage of phenindione. The " thrombotest " method of controlling therapy was relatively insensitive to a reduction in Christmas factor, but the value correlated well with the one-stage prothrombin time.

The author concludes that in busy clinical laboratories determination of the one-stage prothrombin time remains the method of choice by virtue of its technical simplicity. *A. Ackroyd*

834. **Platelet and Fibrinogen Survival in Normal and Abnormal States of Coagulation**

E. ADELSON, J. J. RHEINGOLD, O. PARKER, A. BUENAVENTURA, and W. H. CROSBY. *Blood* [*Blood*] 17, 267–281, March, 1961. 10 figs., 37 refs.

The authors review the evidence that utilization of the blood coagulation factors is going on all the time in the body; most of this evidence is indirect, and they set out to test the concept, using tagged platelets and fibrinogen. In experiments at George Washington University Medical School and Walter Reed Army Medical Center, Washington, D.C. survival of the tagged platelets and fibrinogen was measured in normal dogs and human beings and in those whose clotting mechanism was either speeded up

or slowed down. The hypocoagulable state was induced with dicoumarol; hypercoagulability is less easily demonstrated, but it is thought to occur postoperatively and after the injection of adrenaline, so subjects in these categories were tested.

In dogs and human beings platelet survival was found to be shortened in the postoperative state and after adrenaline injection. It is suggested that in the normal subject the curve of platelet survival is exponential, and evidence is given that such a curve is obtained because of random utilization of platelets in a continuous process of coagulation. In hypocoagulable states the curve of platelet survival becomes more nearly linear, because random destruction ceases. Fibrinogen survival is not altered when there is hypercoagulability. *A. Brown*

CHEMICAL PATHOLOGY

835. **The Significance of Estimation of C-Reactive Protein in the Blood of Children with Certain Diseases.** (Значение определения в крови С-реактивного белка при некоторых заболеваниях у детей)
A. P. Slepcov and P. M. Pašinin. *Вопросы Охраны Материнства и Детства* [*Vop. Ohrany Materin. Dets.*] **6**, 49–54, May, 1961. 19 refs.

C-reactive protein was first detected in 1930 by Tillett and Francis in the serum of patients with croupous pneumonia. The uncapsulated Type-II pneumococcus contains a substance C in addition to the previously recognized capsular polysaccharide A and the somatic nucleoprotein B. It is with this substance C (itself most probably a polysaccharide) that C-reactive protein reacts by precipitation. This protein was first isolated in pure form by MacLeod and Avery (*J. exp. Med.*, 1941, **73**, 183) from the serum of rheumatic patients, and in crystalline form by McCarty (*J. exp. Med.*, 1947, **85**, 491) from the pleural exudate in a case of pneumonia. It is found in close union with lipids; on fractionation with ammonium sulphate it is precipitated with the albumin fraction, but on electrophoresis its velocity corresponds to that of the γ globulins. Various authors have reported that it appears in the blood serum of men and experimental animals some 12 to 18 hours after the injection of such substances as typhoid vaccine, milk, magnesium salts, and gold preparations. Recovery from the pyrogenic action is accompanied by the disappearance of C-reactive protein, which is absent from the blood of healthy persons. Certain authors suggest that it results from the breakdown of mesenchymal tissue, while others regard it as a precursor of antibodies.

In the present investigation the serum of 247 children with various diseases, including 79 with rheumatism (53 in the acute phase) and 32 with infective hepatitis, was repeatedly tested for C-reactive protein during their illness. The method employed was precipitation in capillary tubes, using rabbit serum immunized to the protein, 0·2 to 0·4 ml. of the patient's blood being collected in a micro-pipette and allowed to clot. The immune serum was drawn up a capillary tube for one-third of its length followed by an equal length of the patient's serum, no air-bubble being allowed to intervene in order that the two sera could mix freely. The mixture, after being rolled and rotated for a few minutes, was left in a vertical position for 16 to 18 hours, by which time the interreaction was complete. The degree of precipitation was measured by the length of the mass of precipitate, a length of 1 mm. being recorded as "a trace", 1 to 2 mm. as "weak", 2 to 3 mm. as "positive", and 4 mm. or over as "strongly positive". The reaction was positive in the sera of patients with acute rheumatism, pulmonary inflammation, acute nephrotic nephritis, infective polyarthritis, and infective hepatitis. It was absent or weak in allergic diseases such as asthma and in chronic tonsillitis (thus making an important distinction from those cases developing rheumatism). Other authors have reported its absence in congenital heart disease in the absence of infection. In the cases of infective hepatitis the test was positive in 50% of patients in the first week, in 37·5% in the 2nd week, in 15·6% in the 3rd week and in only 9% (3 very severe cases) in the 4th week. The test can be carried out at any temperature from 4° to 37° C., any variation between these limits having no influence on the rate of precipitation. Its high sensitivity, technical simplicity, and close correspondence with the clinical course of the disease render it a valuable supplementary test in clinical and ambulatory practice. *L. Firman-Edwards*

836. **Urinary Acid Mucopolysaccharide Excretion in Liver Damage**
H. Kawata, T. Koizumi, R. Wada, and T. Yoshida. *Gastroenterology* [*Gastroenterology*] **40**, 507–512, April, 1961. 4 figs., 27 refs.

Connective tissue contains a number of acid mucopolysaccharides as ground substance, the chemical structure of these being well known. The concentration of these acid mucopolysaccharides (A.M.) in the serum and urine has been shown to be increased during rapid growth in children and also in patients with lupus erythematosus, rheumatoid arthritis, leukaemia, and other malignant diseases. In view of several reports that these saccharides are produced in increased amounts in the liver when fibrous tissue is formed in cirrhosis the present investigation was undertaken at Osaka University School of Medicine, Japan, in an attempt to determine whether the urinary excretion of A.M. in patients with liver disease reflected the metabolic state of fibrous tissue in the liver. The authors therefore compared this value in 65 healthy individuals ranging in age from 2 to 75 years with that in 45 patients with liver disease. In addition A.M. excretion was determined in rats poisoned by injections of carbon tetrachloride, samples of urine being collected for analysis before and after liver damage had occurred.

It was found that urinary A.M. excretion was increased in most cases of chronic hepatitis, in active cirrhosis with enlarged liver, and even in 3 out of 4 patients with obstructive jaundice. On the other hand urinary A.M. excretion was reduced in patients with cirrhosis and a shrunken liver and in primary cancer of the liver. It was of interest that in 4 cases of acute hepatitis the results

were within normal limits, possibly indicating that connective tissue metabolism is not seriously affected in the early stages of liver damage. In the rats the chronic liver damage caused by the injection of carbon tetrachloride was associated with an increased urinary A.M. excretion. Although these findings are not pathognomonic, the authors conclude that they "encourage the hope that further studies on the qualitative differences in acid mucopolysaccharides in patients with liver disease may yield considerable insight into the early detection of fibrotic or cirrhotic changes in the liver".

H. Lehmann

MORBID ANATOMY AND CYTOLOGY

837. **Morbid Anatomy and Histology of Influenza in Adults.** (Патологоанатомическая характеристика гриппа у взрослых (По материалам 1959 г.))
A. P. Avcyn and T. G. Terehova. *Архив Патологии* [*Arh. Patol.*] **23**, 3–14, No. 4, 1961. 12 figs., 22 refs.

The authors report the post-mortem findings in 60 adult patients who died during the influenza epidemic of January and February, 1959. Primary changes, attributable to the virus itself, were observed in those dying within the first 2 days from onset and were as follows: (1) paralytic hyperaemia of the vessels in the mucosa of the respiratory tract; (2) degeneration, necrobiosis, and desquamation of the respiratory epithelium; (3) stasis and hyaline thrombi in the pulmonary capillaries; (4) detachment of the hyaline membrane of the alveolar walls; (5) focal oedema and haemorrhages in the lung parenchyma; (6) haemorrhages into the tracheal mucosa; (7) oedema and early degenerative changes in the elastic framework of the lung; (8) swelling of reticulin fibres in the alveolar and bronchial walls; (9) early dystrophic changes in the nervous apparatus of the respiratory system; (10) micro-necroses in the alveolar walls; (11) acute atonic dilatation of the bronchial lumen; (12) circulatory disturbances and dystrophic changes in all internal organs and in the central nervous system; (13) acute cerebral oedema; and finally (14) focal subarachnoid haemorrhages.

In patients dying after the 2nd day changes due to secondary infection with coccal or bacterial organisms made their appearance (the toxic-septic stage), while the third stage was marked by the development of complications. The rapid passage from the first to the second stage emphasizes the necessity for early antibiotic prophylaxis.

A. Swan

838. **Studies on Hepatic Fibrosis**
H. Popper, F. Paronetto, F. Schaffner, and V. Perez. *Laboratory Investigation* [*Lab. Invest.*] **10**, 265–290, March–April, 1961. 26 figs., 45 refs.

For this study, carried out at the Mount Sinai Hospital, New York, samples of liver tissue were obtained by biopsy from healthy subjects and either by biopsy or at necropsy from patients with a wide variety of hepatic disorders; livers from normal rats and from rats exposed to hepatotoxic substances were also studied. Using conventional histological methods two series of sections, 5 μ and 1 μ in thickness respectively, were examined by light and also by electron microscopy to investigate the distribution and formation of reticulum and collagen fibres with particular regard to three areas, namely, within the lobule, around the cholangioles (ductules), and within the portal tracts.

In normal livers there was inside the lobules a framework of argentaffin fibres forming a continuous line between the liver cell plates and the sinusoids; in the ultrathin sections (1 μ) the fibres appeared to be sparse and under the electron microscope were rare. They presented an appearance of uniform width (250 to 300 Å.) with a periodicity of about 600 Å.; there was no basement membrane. Around the cholangioles there was a basement membrane, which in turn was surrounded by a varying number of fibrils with a periodicity of 600 Å. In the portal tracts the fibres formed a loose network between the vessels and ducts.

In cases of mild acute liver damage the fibres were not greatly altered, but in livers showing fatty metamorphosis the argentaffin fibres appeared to be farther apart than normal. In regenerative nodules present in cirrhotic livers the reticulum network was sparse and appeared to be compressed around the nodules. In cases of severe acute liver-cell injury, as for example in viral hepatitis, or of protracted liver damage (as in chronic fatty metamorphosis) the fibres on the sinusoidal wall of the liver cell were increased in number and thickened. In zones of extensive parenchymal collapse typical fibroblasts were sometimes noted, but these were usually absent in other conditions. Around proliferating cholangioles there was an increase in the number of both reticulin and collagen fibres, notably in viral hepatitis, but also in most types of cirrhosis. Finally five types of portal-tract fibrosis are described: (1) stellate fibrosis, with collagen membranes extending into the parenchyma, a type seen especially in chronic fatty metamorphosis; (2) diffuse fibrosis, with uniform enlargement of the tracts, a condition seen in portal inflammation, haemochromatosis, and biliary cirrhosis; (3) concentric fibrosis, seen in biliary obstruction; (4) fibrosis following collapse of the parenchyma; and (5) irregular fibrosis, as in healing granuloma.

[It is difficult in an abstract to do justice to a paper devoted to a description of morphological appearances, particularly one illustrated by numerous photomicrographs. The present study is no exception and for further details the original paper must be consulted.]

W. H. Horner Andrews

839. **The Pathology of 111 Cases of Primary Hepatic Malignancy Collected in the Liverpool Region**
A. H. Cruickshank. *Journal of Clinical Pathology* [*J. clin. Path.*] **14**, 120–131, March, 1961. 21 figs., 15 refs.

In this paper are analysed 111 cases of primary malignant hepatic tumour recorded in the files of the Liverpool Cancer Control Organization during the years 1947–59. There were 108 cases of carcinoma, 2 of sarcoma, and one of mixed-cell tumour. Sections or preserved tissue with short clinical or necropsy notes were available in all cases. A further 12 cases were discarded because of insufficiency of available evidence. Based on the 60,600

necropsies recorded in the relevant period, the 88 cases of carcinoma of the liver in which necropsy was performed represent an incidence of 0·145%, which is almost exactly the same as for Europe generally.

Among the 108 cases of carcinoma there was a well-marked sex difference, males (82) predominating, especially with regard to liver-cell tumours. The ages ranged from 2 to 88 years, but the incidence was highest in the 6th decade. The occupation of 18 of the 26 women was given as housewife, and of 17 of the men as seafarer. Portal cirrhosis (58 cases) and haemochromatosis (7 cases) were the chief predisposing factors, especially in the males; in 40 cases no predisposing lesion was recorded. Ascites was present in 61 cases and jaundice in 44. Although some splenic enlargement was the rule, it was of clinically significant degree in only 4 cases. Microscopically, of the 108 cases, 80 (65 male and 15 female) were found to be of liver-cell carcinoma and 21 (12 male and 9 female) of cholangiocarcinoma; the remaining 7 cases were of indefinite appearance. Liver-cell carcinoma was about 4 times more frequent than carcinoma of the hepatic ducts, but, despite its tendency to permeate veins within the liver, it appeared to be slightly less malignant in its behaviour than cholangiocarcinoma. It was an incidental finding, without metastases, in 8 of the 88 necropsy cases, and when metastasis had occurred lymph nodes were affected more commonly than organs involved by spread via the blood stream. In nearly every one of the 21 cases of carcinoma of the intrahepatic bile ducts the tumour was the main cause of death. Haemorrhage, mainly from oesophageal varices or into the peritoneal cavity, was common.

The author found insufficient information to indicate whether infective hepatitis or alcoholism had played an important part in the aetiology of any of the cases. In general, these cases from Merseyside tended to be similar in type and behaviour to those studied in the U.S.A. and to a lesser extent to resemble the Oriental and African type of case. *G. Clayton*

840. **Pathogenesis of Regional Enteritis. Based upon Histologic Study of Forty Cases**
R. W. Ammann and H. L. Bockus. *Archives of Internal Medicine* [*Arch. intern. Med.*] **107**, 504–513, April, 1961. 14 figs., 21 refs.

In a study of the pathogenesis of regional enteritis carried out at the University of Pennsylvania, Philadelphia, an average of 8 or 9 sections of intestine were cut from each surgical specimen from 40 cases of regional enteritis, stained with haematoxylin and eosin, and examined. It is concluded that the changes in the proximal, pre-ulcerative segments (mucosal distortion, infiltration of the lamina propria with P.A.S.-positive macrocytes, and the presence of "Brunner glands") are apparently due largely to lymphoedema, and that these effects are similar to those produced experimentally by lymphatic obstruction. Ulcers, thickening of the muscularis mucosae, and displacement of mucosa with the submucosa or intestinal lumen are related to deformation of the Kerckring folds. It is considered that the early pathological changes in regional enteritis are best explained as direct or indirect sequelae of oedema of the small intestine, the cause of which is unknown.
A. Wynn Williams

841. **The Fine Structure of Human Atherosclerotic Lesions**
J. C. Geer, H. C. McGill Jr., and J. P. Strong. *American Journal of Pathology* [*Amer. J. Path.*] **38**, 263–287, March, 1961. 15 figs., 43 refs.

Electron microscopy of elastic and muscular arteries in the normal dog and rat disclosed the fine structure of cellular and connective tissue elements to be similar to that described for endothelium, smooth muscle, elastic fibers and collagen fibers in other organs. Human arterial tissue procured at necropsy, fixed in buffered formalin and postfixed in osmium tetroxide was, with certain limitations, satisfactory for electron microscopy. This method was used in the study of human atherosclerotic lesions with particular emphasis on early fatty streaks in the coronary arteries and the aorta.

In young individuals the lipid in small intimal fatty streaks lay predominantly in smooth muscle cells and had a reticulated structure. In more advanced streaks from older individuals and in fibrous plaques, intracellular lipid appeared either as clear vacuoles or dense homogeneous inclusions. The lipid-containing cells in more advanced lesions, though occasionally identified as smooth muscle, were often not identifiable. Some smooth muscle elements contained such large numbers of lipid inclusions that they appeared to be in transition to foam cells.

The existence of cytoplasmic lipid inclusions in smooth muscle was interpreted as evidence of lipid synthesis *in situ*. The initial lipid deposition in human atherosclerosis could, therefore, be due to an alteration in the smooth muscle metabolism, causing intracellular lipid to accumulate in abnormal amounts. The different forms of lipid in the various lesions were believed to be due to chemical differences, principally degrees of unsaturation.

In the more advanced stages of human atherosclerosis there were structures in the interstitial tissue thought to represent lipid and other forms representing cholesterol clefts. There were also cells with degenerative cytoplasmic changes. The hypothesis is proposed that degeneration of lipid-containing cells may lead to the extravasation of lipid particles into the extracellular spaces. This, in turn, may serve as the stimulus to fibrosis and the progression of lesions to more advanced stages.—[Authors' summary.]

842. **The Frequency of Aschoff Bodies in Atrial Appendages of Patients with Mitral Stenosis. Relationship to Age, Atrial Thrombosis, and Season**
B. H. Ruebner and J. K. Boitnott. *Circulation* [*Circulation*] **23**, 550–561, April, 1961. 10 figs., bibliography.

A study is reported from the Johns Hopkins University School of Medicine and the Johns Hopkins Hospital, Baltimore, of the incidence of Aschoff bodies in the atrial appendage of 316 patients operated on for mitral stenosis who were considered clinically to show no evidence of

active rheumatism. Hearts showing mitral stenosis obtained at necropsy on 25 patients and atrial appendages similarly obtained from 20 other subjects were also studied.

The 316 atrial appendages were divided histologically into three groups: (1) those with typical Aschoff bodies fulfilling the criteria of Gross and Ehrlich; (2) those with non-specific granulomata consisting of foci of inflammatory cells in the endocardium and subendocardium but without the characteristic nuclei of Aschoff cells; and (3) appendages without a lesion. Aschoff bodies were observed in 130 (41%) of the atrial appendages, non-specific granulomata in 72 (23%), and endocardial thrombosis in 76 (25%).

In patients with auricular fibrillation the incidence of Aschoff bodies depended on the presence or otherwise of atrial thrombosis; thus Aschoff bodies were found in 23 out of 49 patients with fibrillation alone but only in 3 out of 53 with atrial fibrillation and thrombosis. Aschoff bodies occurred with equal frequency in males and females, but were commoner in younger patients, the incidence being 66% in the age group 15 to 20 years and 44% in the age group 55 years and over. A seasonal variation in the incidence of Aschoff bodies was also observed, 25% of the specimens being positive in June and 65% in September.

It is concluded that there is no precise correlation between the clinical evidence of activity and the presence or otherwise of Aschoff bodies; that atrial thrombosis rather than concurrent fibrillation is the principal factor in the lowered incidence in certain patients; and that the seasonal incidence may be due to the fact that the rheumatic process is intermittently active in patients subjected to mitral valvotomy, in spite of the absence of clinical manifestations. *Hewett A. Ellis*

843. A Quantitative Method for Studying Tumour Cells in Blood

S. W. A. KUPER, J. R. BIGNALL, and E. D. LUCKCOCK. *Lancet* [*Lancet*] **1**, 852–853, April 22, 1961. 2 figs., 8 refs.

The authors, working at the Institute of Diseases of the Chest and the Brompton Hospital, London, have evolved a new technique for removing erythrocytes and polymorphonuclear leucocytes from the blood so that tumour cells can be identified and counted among the remaining cellular elements.

The technique involves adding 100 mg. of carbonyl iron to 10 ml. of heparinized fresh blood. Polymorphonuclear leucocytes ingest the iron and after 30 minutes are removed with a magnet. The erythrocytes are readily lysed by a brief exposure to saponin, and after centrifugation the residual cells are fixed (10 ml. of a freshly prepared solution of 10% formalin and 10% acetic acid in 50% alcohol being used) and filtered off on to a millipore membrane. The membrane is stained with haematoxylin and eosin, cleared, and mounted in a synthetic resin.

The method is simple, but the identification of unusual cells as having originated from tumours is difficult unless, as in the case of melanoma, the cells have clearly identifying characteristics. The authors therefore prefer to classify cells as "probably from a tumour", rather than as definite tumour cells. "Highly suggestive" cells were found in peripheral blood from 3 out of 36 patients with bronchial carcinoma and in pulmonary vein blood from 3 out of 10. However, suggestive cells were seen in 1 out of 78 samples from patients without other evidence of neoplasm.

The authors state that more knowledge of the variety and morphology of unusual cells in the blood is required before tumour cells can be identified with certainty.

H. Caplan

844. Centrifugal Metastasis in Lung Cancer

W. I. B. ONUIGBO. *British Journal of Diseases of the Chest* [*Brit. J. Dis. Chest*] **55**, 86–90, April, 1961. 3 figs., 39 refs.

A study of the literature of cancer of the lung suggests that the more distant an organ is from the primary growth, the less often is it the site of metastasis. This pattern would not, however, be expected if it is accepted that visceral metastases are haematogenous. In order to examine the problem whether pulmonary cancer spreads centrifugally to the viscera the author, at the University and Western Infirmary, Glasgow, has surveyed the necropsy records of 6,000 cases of lung cancer collected from medical schools in Britain and another 6,000 cases collected from the literature. In both series the occurrence of centrifugal metastasis was apparent; thus the liver was the site of secondary deposit in 4,841 of the 12,000 cases, the adrenal in 3,906 cases, and the kidney in 2,175 cases, giving percentages of 40, 32·5, and 18 respectively. Similarly, study of the para-aortic lymph nodes showed the proximal nodes to be earlier and more grossly involved than the more distal ones.

It is suggested that lymphogenous spread is compatible with, and accounts for, discrete metastases in the lymph nodes and abdominal viscera. *A. W. H. Foxell*

845. Renal Glomerular and Vascular Lesions in Prediabetes and in Diabetes Mellitus: a Study Based on Renal Biopsies

A. DAYSOG JR., H. L. DOBSON, and J. C. BRENNAN. *Annals of Internal Medicine* [*Ann. intern. Med.*] **54**, 672–684, April, 1961. 4 figs., bibliography.

The histological appearances of the kidney in prediabetes and in overt and latent diabetes were studied at Baylor University College of Medicine, Houston, Texas, in 70 renal biopsy specimens from 62 patients. The diagnosis of prediabetes was based on the results of the glucose tolerance test after cortisone provocation and suggestive evidence such as a family history of the disease, the presence of premature vascular degeneration, and overweight.

Kidney tissue from all 62 patients showed varying degrees of diffuse thickening of the glomerular basement membrane; 37 of the patients were considered to have minimal nephropathy. In 4 patients in whom these changes were least obvious under light microscopy the basement membrane measured 6,000 to 9,000 Å. by electron microscopy, about 2 to 3 times the normal thick-

ness. Glomerular changes were considered to be moderate in 10 patients and marked in 15. One example of each was studied by electron microscopy, confirming the observations by light microscopy. The Kimmelstiel–Wilson lesion or nodular glomerular sclerosis was found in 31 of the patients and exudative "fibrinoid" lesions in 38, including prediabetics and patients with adequately and inadequately controlled disease.

The authors state that the renal changes observed seem to be a constant accompaniment of the diabetic syndrome; they were not found in approximately 300 kidney biopsy specimens from non-diabetics. Their findings suggest that nephropathy in diabetics is virtually inevitable and may precede the metabolic defects. The renal lesions may progress rapidly in well controlled diabetics or slowly in badly controlled cases. It is postulated that the nephropathy and the carbohydrate defect of diabetes mellitus are independent of each other, but evolve from the same basic abnormality.

H. Caplan

846. **Renal Biopsy in Gout**

D. GREENBAUM, J. H. ROSS, and V. L. STEINBERG. *British Medical Journal* [*Brit. med. J.*] **1**, 1502–1504, May 27, 1961. 3 figs., 14 refs.

The association of renal disease with gout is well recognized, but the pathogenesis of the kidney disorder has not been clearly defined. This study of renal biopsy specimens, reported from the London Hospital, was designed to determine if very early lesions could be identified and if they could be correlated with the clinical state of the patients. Renal biopsy was performed on 11 men and one woman, aged 40 to 69 years, with a history of attacks of gouty arthritis ranging from 4 to 38 years. Renal function tests were also carried out. Only 2 of these patients were known to have evidence of renal impairment, but 8 others were found to have proteinuria and/or impairment of renal function and 6 had disorders of renal structure.

The study provided no conclusive information about the production of gouty nephropathy. It is thought that possibly the earliest renal lesion is slowly progressive tubular damage accompanied by interstitial reaction. In time tubular atrophy would develop with or without coincidental infection and produce the final picture of "interstitial nephritis". *A. W. H. Foxell*

847. **Cerebrovascular Disease: VIII. Role of Nutritional Factors**

A. B. BAKER, J. KINNARD, and A. IANNONE. *Neurology* [*Neurology* (*Minneap.*)] **11**, 380–389, May, 1961. 2 figs., bibliography.

The authors of this paper from the University of Minnesota Medical School, Minneapolis, in an attempt to determine the influence of obesity, malignancy, and diabetes on the development of atherosclerosis, studied the degree of atherosclerotic change in the arteries of the circle of Willis and their major branches in 1,175 consecutive necropsies. To elucidate the nature of the degenerative process 500 large arteries of the circle of Willis were examined histologically, and the findings support the concept that hyperplasia of the intimal connective tissue is the primary change and that fatty deposits are secondary to these abnormalities.

The incidence of atherosclerotic change was not higher in obese subjects except in the 6th and 7th decades of life, where atherosclerosis was 2 to 2½ times more common in obese than in underweight individuals. This trend was reversed in the 8th decade. It is suggested that hypertension, which is more frequent in the obese, is responsible for the increased incidence of atheroma in this group.

Of the 1,175 cases studied, death was due to malignant disease in 364. Only 40% of these patients were underweight. No cerebral atheroma occurred in this group until the 5th decade, and severe degrees were not encountered until the 7th decade. It is suggested either that atheroma regresses in the presence of malignant disease or that patients with malignant disease have an inherent protection from atheroma.

Over the age of 40 the incidence of atherosclerosis in diabetics was twice as high as in the general population.

H. S. Schutta

IMMUNOPATHOLOGY

848. **Direct Anti-globulin-consumption Test for Detection of Immune Antibodies**

D. NELKEN, J. GUREVITCH, and N. GILBOA-GARBER. *Lancet* [*Lancet*] **1**, 742–744, April 8, 1961. 11 refs.

A new direct anti-globulin consumption test has been developed for the detection of immune antibodies. This test is relatively simple and gives easily reproducible results. Pure suspensions of erythrocytes, leucocytes, and thrombocytes from the blood to be examined are added to an anti-globulin serum of known titre and are left at room temperature for 30 minutes. The supernatant fluid is then tested for its anti-globulin titre against red blood-cells coated with incomplete anti-D serum. The difference in the titre of the anti-globulin serum before and after the addition of the examined cells is taken as a measure of their sensitisation. If the cells are heavily coated, complete consumption of the anti-globulin takes place.

This test proved most satisfactory in cases both of acute and of chronic idiopathic thrombocytopenic purpura. The test was also satisfactory in cases of thrombotic thrombocytopenic purpura, pancytopenia, and systemic lupus erythematosus. Positive results were obtained in cases of leukaemia and of generalised carcinomatosis. The nature of the coating globulin is not yet known, and it cannot be said with certainty that it is a true antibody.—[Authors' summary.]

849. **Incidence of Haemagglutinating and Complement-fixing Antibodies**

G. L. ASHERSON and O. BROBERGER. *British Medical Journal* [*Brit. med. J.*] **1**, 1429–1433, May 20, 1961. 20 refs.

It was shown by Broberger and Perlmann (*J. exp. Med.*, 1959, **110**, 657; *Abstr. Wld Med.*, 1960, **28**, 29) that most sera from children with ulcerative colitis pre-

cipitated an antigen extracted with phenol-water from normal human colon and agglutinated erythrocytes coated with this antigen. The present authors, working at the Canadian Red Cross Memorial Hospital, Taplow, and the Wenner–Gren Institute, Stockholm respectively, have extended this work, adding further immunological tests and other diseases.

They found that of 14 children with ulcerative colitis, the sera of 12 agglutinated colon-antigen-coated erythrocytes to titres of from 1:64 to 1:256. Among adults with ulcerative colitis antibodies were less frequent (in 13 out of 36 cases) and the titres lower (1:4 to 1:64). Of 42 control subjects with acute bacterial infections, only one showed haemagglutinins, to a titre of 1:4. Reactions were less frequent and were also weaker against erythrocytes coated with antigen extracted from human liver in the same way.

Complement-fixing antibodies to antigens extracted with sucrose solution from rat liver or kidney were found in 4 out of 13 children with ulcerative colitis—a low but still significant incidence. Of the 36 adults, 2 gave a positive reaction, an incidence not significantly different from that in the controls (1 out of 42).

Some of the results in other diseases are summarized in the table below. Isolated cases of rheumatic fever, Reiter's disease, and hyperparathyroidism also showed haemagglutinins, but no complement-fixing antibody. The widespread occurrence of autoimmune antibodies in certain diseases is thus confirmed, and the authors discuss various ways in which this might have arisen [without, however, coming to any satisfactory conclusion].

Disease	No. of Cases	Complement-fixation with Rat-kidney Antigen. Titres 1/16 to 1/256+. No. Positive	Haemagglutination with Human Colon Antigen Titres 1/2 to 1/64. No. Positive
Systemic lupus erythematosus ..	14	13	5
Hepatic cirrhosis ..	28	6	8
Rheumatoid arthritis	26	6	4
Nephrosis	9	2	0
Syphilis	6	5	0
Lupoid hepatitis ..	4	4	1
Biliary cirrhosis ..	3	3	0
Rheumatoid arthritis with lung fibrosis	2	2	0
Acute bacterial infections	42	1	1

M. C. Berenbaum

850. **Determination of Antibodies to Kidney Tissue: the Complement-consumption Test**

V. CHUDOMEL and Z. JEŽKOVÁ. *Lancet* [*Lancet*] 1, 965–967, May 6, 1961. 4 figs., 15 refs.

The authors, who work at the Institute of Haematology and Blood Transfusion, Prague, have adapted the quantitative complement fixation test for the detection of antibodies against human kidney, in that instead of adding guinea-pig complement they use the complement in the test serum. In this method uninactivated human serum was mixed with saline extract of human kidney (which was either stored frozen or lyophilized), while saline served as a control. After incubation the serum was diluted and its complement titre determined. A difference of two tubes between the control tube and the antigen tube was regarded as a weak positive result. The complement consumption (amount of complement fixed) increased with the amount of antigen used and then levelled off. As the amount of antibody was reduced the complement consumption fell and then remained stationary.

Application of the test to the sera of 351 normal subjects showed a positive result in only 4% of cases, while of 64 sera of patients with miscellaneous (non-renal) diseases, 6% were positive. In contrast 31 sera (65%) of 48 children aged 2 to 15 years with renal disease were positive, a positive result being obtained in 23 (85%) of 27 with acute glomerulonephritis, 5 (100%) of 5 with chronic glomerulonephritis, 4 (80%) of 5 with the nephrotic syndrome, and 4 (36%) of 11 with miscellaneous renal disorders. The authors conclude that the complement consumption test provides a method for detecting antibodies to kidney tissue.

G. L. Asherson

851. **Immunology of Glomerulonephritis**

V. CHUDOMEL, Z. JEŽKOVÁ, L. PÁVKOVÁ, and E. KRATKOVÁ. *Lancet* [*Lancet*] 1, 968–970, May 6, 1961. 4 figs., 5 refs.

In this immunological study of the sera of 48 children with renal disease, using the complement consumption test [see Abstract 850] and the collodion agglutination test, the authors found that of 27 patients with acute glomerulonephritis, a positive result was obtained by the complement consumption test in 25 and by the collodion agglutination test in 17. All of 5 patients with chronic glomerulonephritis gave a positive result by the complement consumption test and 2 by the collodion agglutination test, while for 5 children with the nephrotic syndrome the corresponding figures were 5 and 3 respectively. In 5 out of 11 patients with miscellaneous renal disease the consumption reaction was positive in 5 and the collodion reaction positive in 3; of these 5 patients, one had the hepato-renal syndrome, 3 pyelonephritis, and one tuberculous renal disease.

Agreement between the results of the two tests was good in all groups. In 8 patients with acute glomerulonephritis the antibodies declined towards negativity in parallel with clinical improvement. In some cases, however, the antibodies persisted without diminution, corresponding to the clinical course of acute glomerulonephritis, in which signs of an active process remain for a long time, while in others the titre bore no obvious relation to the clinical picture. The authors conclude that kidney antibodies occur in renal disease, but they were unable to decide whether these antibodies are responsible for the disease or merely secondary to it.

G. L. Asherson

852. **Current Concepts of Autoimmunization: an Interpretive Review**

W. DAMESHEK, R. SCHWARTZ, and H. OLINER. *Blood* [*Blood*] 17, 775–783, June, 1961. 1 fig., 34 refs.

Microbiology and Parasitology

853. **Purified Poliomyelitis Vaccine—Clinical Appraisal**
C. WEIHL, D. CORNFELD, H. D. RILEY, N. HUANG, and H. CRAMBLETT. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **176**, 409–412, May 6, 1961. 2 figs., 11 refs.

Although the efficacy of Salk poliomyelitis vaccine has been estimated to range between 80 and 90%, more than 5,000 cases of paralytic poliomyelitis were reported in the U.S.A. in 1959. Failure by Salk vaccine to eradicate paralytic poliomyelitis appears to stem from two factors —failure to apply the vaccine as completely as necessary and failure of the vaccine itself to protect all individuals, due in part to variations in antigenic potency from lot to lot. Recently a new purified concentrated poliovirus vaccine containing precisely standardized optimal amounts of poliovirus antigen has been developed commercially under the name of " purivax ". In the purification process the vaccine is freed of all serologically detectable monkey kidney substance and essentially all other non-viral contaminating substances present in the ordinary crude commercial Salk vaccine.

The authors report the serological responses to two 0·5-ml. doses of this purified vaccine given a month apart in 53 serologically negative children ranging in age between 3 months and 7 years and compare them with those obtained with two 1-ml. doses of some exceptionally potent lots of Salk vaccine in 41 comparable children. With the purified vaccine the proportions of children responding to vaccination with an antibody titre of 1:4 or greater were 98% (Parker) and 94% (Mahoney) for Type 1, 100% for Type 2, and 92% for Type 3, while with the Salk vaccine they were 76%, 71%, 98%, and 80% respectively. The proportion converted from triply negative to triply positive was 92% for the purified and 63% for the crude vaccine. The geometric mean titres achieved with purified vaccine were 1·5 to 5 times higher than with crude vaccine.

The authors believe that this purified vaccine answers the urgent need for a poliomyelitis vaccine that will consistently, rapidly, and safely immunize essentially all recipients against all 3 poliovirus types. It will also eliminate the possibility of any sensitivity reactions.

A. Ackroyd

854. **Some Data on the Survival of *Rickettsia burneti* on Objects in the External Environment.** (Некоторые данные о выживаемости *R. burneti* на предметах внешней среды)
V. N. PAUTOV. *Вопросы Вирусологии* [*Vop. Virusol.*] **6**, 217–219, March–April, 1961. 29 refs.

The considerable powers of resistance of *Rickettsia burneti* in fluids and tissues is well known, but little information is available on its survival on inanimate objects. In the present investigation the duration of survival of this organism on cotton and woollen materials, seeds, stainless steel, and dry and damp soil at temperatures of 20° and 4° C. was examined, using the Greta strain of the rickettsia grown in chick embryos. The culture in a concentration of $10^{9\cdot5}$ to 10^{11} ID_{50} (for guinea-pigs) per ml. was applied to the various test objects in quantities of 1·0 or 2·5 ml. and allowed to soak into or dry on the surface. The objects were then placed in flasks which were filled with a quantity of phosphate buffer at *p*H 7·4, the quantity of buffer used being 100 times that of the infecting fluid. The flasks were shaken continuously at the rate of 60 to 100 times per minute for 3 hours, the fluid then centrifuged for 10 minutes at 600 r.p.m., and the supernatant used for titration on guinea-pigs, taking the dilution of *R. burneti* as 1 in 100. Survival was determined after 10, 20, 30, 90, 120, and 180 days at 20° C. and after 3, 6, and 12 months at 4° C.

On all types of material kept at 20° C., with the exception of damp soil, the concentration of *R. burneti* decreased 10- to 100-fold after 10 to 20 days, while after 30 to 90 days the decrease was of the order of 10^4 to 10^6. In damp soil the decrease in the number of viable rickettsiae did not exceed 10- to 100-fold after 180 days. On objects maintained at a temperature of 4° C. the concentration of *R. burneti* fell by only 10 to 100 times after 3 to 6 months and after 12 months the decrease was of the order of 10^4 to 10^5. The long survival of *R. burneti* on inanimate objects here demonstrated points to some sources of Q-fever infection in the laboratory.

K. Zinnemann

855. **Serological Investigations of Atypical Acid-fast Bacilli**
A. BECK. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **82**, 45–51, 1961. 21 refs.

The investigation herein reported from Paddington General Hospital, London, was designed to demonstrate the relationship, if any, between the antigens of photochromogenic " atypical " acid-fast bacilli, saprophytic acid-fast bacilli, and human *Mycobacterium tuberculosis*. Purified protein derivatives were prepared from three strains of Group-I photochromogens, and one strain each of *Myco. tuberculosis* var. *hominis* H37Rv, *Myco. smegmatis*, and *Myco. phlei*. Sheep erythrocytes were sensitized with these extracts and titrations of antibody in rabbit antisera prepared against the strains were carried out by a technique involving a haemolytic end-point. Absorption and inhibition tests were also performed.

The findings indicate that there is most probably one antigen which is common to all the four species involved. In addition, the human mycobacterium and the atypical strains appear to have another antigen in common, while the atypical strains possess a third antigen peculiar to themselves.

The author emphasizes the heat lability of some of these antigens and stresses the need for avoiding heat in their preparation.

John M. Talbot

Pharmacology

856. **Depression of Food Intake Induced in Healthy Subjects by Glucagon**
S. B. PENICK and L. E. HINKLE JR. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 893–897, May 4, 1961. 9 figs., 8 refs.

Glucagon, the hyperglycaemic factor of the pancreas, has been found by Schulman *et al.* (*J. appl. Physiol.*, 1957, **11**, 419) to depress the appetite and thus decrease the food intake in man. Its effect used to be attributed to the fact that it causes a significant difference between the blood glucose levels in the peripheral arteries and veins. It has been shown, however, that experimental elevation of this arterio-venous difference by administration of glucose does not adversely affect the appetite. This fact suggests that glucagon depresses the appetite through some property other than its hyperglycaemic one. At the New York Hospital–Cornell Medical Center, therefore, the authors devised acute and chronic experiments to explore the relationship between glucagon, food intake, appetite, and blood glucose concentration in healthy young medical students. It was found that after the intramuscular administration of 1 mg. of glucagon subjects who were offered an appetizing test meal within 2 to 4 hours showed diminished food intake. This was sometimes associated with anorexia or with slight nausea, but frequently it was not. This effect of glucagon upon food intake took place at a time when the absolute blood glucose values and the arterio-venous blood glucose difference had returned to postabsorptive levels. It is therefore thought that the action of glucagon upon food intake is independent of the peripheral blood glucose level. It was noted that gastro-intestinal motility was inhibited at times when symptoms of anorexia or nausea occurred.

It was also established that the long-term administration of glucagon (1 mg. intramuscularly 3 times a day for 6 days) depressed food intake and consequently caused loss of weight. No evidence was found that glucagon has any catabolic activity. It is well known that if food is not taken at the time the peak of hunger has been reached the pangs will diminish with the passage of time. This phenomenon is thought to be partly explained by the fact that glucagon secretion appears to increase as the blood glucose level falls. Whereas insulin decreases the peripheral blood glucose level, stimulating hunger contractions, glucagon causes a rise in the reduced blood glucose level resulting from starvation, thus diminishing the urge to eat. *S. M. Hardy*

857. **The Interaction of Bretylium with Pressor Agents**
D. R. LAURENCE and R. E. NAGLE. *Lancet* [*Lancet*] **1**, 593–594, March 18, 1961. 2 figs.

Frequently hypertensive patients who initially respond to bretylium become tolerant to the drug after a time, and it has been suggested that this might be due to increased sensitivity to adrenaline and noradrenaline. In an attempt to elucidate this matter the authors, at University College Hospital Medical School, London, have investigated the interaction of pressor agents with bretylium, the subjects being healthy volunteers and patients under treatment for hypertension.

The hypertensive effect of adrenaline and noradrenaline was found to be potentiated by bretylium in man as in animals. Steady infusions of low doses of noradrenaline abolished the postural hypotensive effect of bretylium. Phentolamine, an adrenolytic drug, abolished the tolerance to bretylium and restored the postural fall in blood pressure. The response to hypertensin was unaffected by bretylium.

These results are held to suggest that in the tolerant state adrenaline and noradrenaline act as antagonists to the hypotensive action of bretylium. The exact mechanism of this has not yet been elucidated.

G. S. Crockett

858. **The Assessment of Antitussive Drugs in Man**
F. J. PRIME. *British Medical Journal* [*Brit. med. J.*] **1**, 1149–1151, April 22, 1961. 10 refs.

The author, at the Institute of Diseases of the Chest, London, has used a method of inducing cough described by Tiffeneau (*Z. Aerosol-Forsch.*, 1955, **4**, 116; *Dis. Chest*, 1957, **31**, 404) to compare the antitussive potency of codeine phosphate and pipazethate hydrochloride (" selvigon "). In preliminary trials no cough followed the inhalation of a 1% aerosol of acetylcholine chloride for 1½ minutes by 12 non-smokers who normally had no cough. On the other hand coughing was induced by this method in 12 subjects who smoked an average of 20 cigarettes a day and who normally had a slight cough, and this group was therefore used in the investigation.

Each subject breathed the aerosol solution for 1½ minutes or until coughing began, and the number of coughs during the ensuing 20 minutes was counted. He then took a tablet of either pipazethate (20 mg.) or codeine (16 mg.) or an inert placebo tablet, and after a 20-minute interval the test was repeated. Statistical analysis showed that the two active substances were about equally effective in protecting against the cough produced by inhalation of an acetylcholine chloride aerosol. *G. S. Crockett*

859. **Thrombolysis of the Experimental Radioactive Pulmonary Embolus: Its Demonstration with the Use of Several Agents**
M. HUME. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 471–475, March 9, 1961. 8 figs., 8 refs.

In this study of the efficacy *in vivo* of thrombolytic agents in dissolving blood clots, carried out at Yale University School of Medicine, clots prepared from dog's blood to which human plasminogen and bovine fibrino-

gen labelled with radioactive iodine (^{131}I) had been added were inserted via the inferior vena cava into the circulation as a pulmonary embolus. The activity of the mixture before clotting was about 2 μc. per ml. The clots were prepared in 16-mm. glass tubing, washed, and then placed in a large volume of buffered saline solution for 48 hours to allow loosely bound ^{131}I to diffuse out. The thrombolytic agents tested, namely, urokinase-activated plasminogen, streptokinase, and plasmins A, B, and C, were injected into a femoral vein 20 hours after implantation of the embolus, by which time spontaneous changes in embolus weight and radioactivity had usually passed their maximum. To determine the changes taking place in the status of the embolus measurements were made at various intervals after embolization of (1) the level of radioactivity in the blood, (2) radioactivity over the lateral aspect of the thorax, determined by means of a probe-type scintillation counter positioned over the point of maximum radioactivity, and (3) radioactivity in the urine. All experiments were completed in 48 hours.

None of the agents tested produced thrombolysis in every experiment, although urokinase, streptokinase, and plasmins B and C did dissolve the embolus partly in most tests. Plasmin A, however, gave equivocal or no evidence of thrombolysis when used in the recommended dosage. It is suggested that these results emphasize the fact that not only the agent employed but other factors as well must be considered in developing a predictable method of treatment of thrombo-embolic disease.

I. M. Rollo

860. **Clinical Observations on the Diuretic Effect of Hydrochlorothiazide**

G. Czoniczer, E. Burwell, J. Niles, R. Reider, J. Robinson, and B. F. Massell. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **7**, 396–403, March, 1961. 5 figs., 6 refs.

The diuretic activity of hydrochlorothiazide was studied in a total of 32 patients with fluid retention at the House of the Good Samaritan, Children's Hospital Medical Center, Boston, and the Cape Cod Hospital, Hyannis, Massachusetts. Of the patients, 26 were females and 6 males, and their ages ranged from 5 to 76 (average 44) years. In 12 out-patients with congestive heart failure the effect of hydrochlorothiazide, 100 mg. daily, was compared with that of chlorothiazide, 1 g. daily, the two drugs being given alternately for periods of one week at a time. Scattergrams of 23 comparisons of change in weight in the 12 patients and of 12 comparisons of average daily urinary output in 6 of them [7 according to the text] showed the diuretic responses to be approximately the same. However, in 4 other patients with congestive heart failure the comparisons, 14 of change in body weight and 8 of change in urinary output, showed hydrochlorothiazide, 150 mg. daily, to have a greater diuretic effect than chlorothiazide, 1·5 g. daily; and 23 comparisons of weight change in 8 patients indicated that the two drugs in dosages of 50 to 75 mg. and 1 g. daily respectively and of 100 to 125 mg. and 1·5 g. daily respectively produced equal diuretic responses. On the other hand with 13 observations of weight change in 5 patients a comparable response appeared to result from hydrochlorothiazide, 125 to 150 mg. daily, and chlorothiazide, 1 g. daily. It is therefore concluded that although the usual therapeutic dosage ratio of hydrochlorothiazide to chlorothiazide is 1:10, there are individual variations in this proportion.

In 4 other out-patients with congestive heart failure hydrochlorothiazide in a dosage of 25 to 100 mg. daily was more effective than ammonium chloride, 3 to 4 g. daily, and in 2 others hydrochlorothiazide in a dosage of 50 to 100 mg. daily produced at least as good a diuresis as acetazolamide, 375 to 1,000 mg. daily. Hydrochlorothiazide was also effective in 4 in-patients, 2 with congestive heart failure and 2 with oedema secondary to corticosteroid therapy in high dosage for rheumatic fever. Fluid retention could not be adequately controlled with the diuretic in only 2 of the whole series of 32 patients studied. Both were in-patients; one had severe congestive heart failure, while the other had disseminated lupus erythematosus with severe renal involvement, which suggested that the action of hydrochlorothiazide could be interfered with by severe kidney damage, as has been reported with chlorothiazide. A fall in mean blood pressure from 180/105 to 150/95 mm. Hg occurred in the only patient with hypertension studied when hydrochlorothiazide was substituted for chlorothiazide. This was the only instance in which the diastolic pressure decreased by 10 mm. Hg or more, whereas the systolic pressure decreased by 10 to 15 mm. Hg in 8 patients and by 20 mm. Hg in one. Bradycardia associated with hydrochlorothiazide therapy was observed in 10 out of 18 patients who had atrial fibrillation and were taking digitalis, the mean reduction in heart rate being from 73 to 59 beats per minute. [A potentiating effect on the action of digitalis with this group of diuretics has frequently been noted previously.] Two patients who had a brisk diuresis while not taking supplementary potassium developed weakness, dryness of the mouth, and muscle pains, and the serum potassium level, estimated in one of them, was reduced to 2·7 mEq. per litre. In 8 further patients there were mild side-effects, mainly fatigue or drowsiness, not necessitating any modification of treatment.

J. J. Segall

861. **Relation between Diuretic Agents and Aldosterone in Cardiac and Cirrhotic Patients with Sodium Retention**

J. P. Thomas and F. C. Bartter. *British Medical Journal* [*Brit. med. J.*] **1**, 1134–1139, April 22, 1961. 6 figs., 36 refs.

From the National Institutes of Health, Bethesda, Maryland, comes this report of a study of the effects of diuretics on the electrolyte excretion in 7 patients—3 with cirrhosis and ascites and 4 with congestive cardiac failure—chosen because their daily sodium excretion was less than 5 mEq. The patients, who were studied in a metabolic ward, were allowed 50 mEq. of sodium a day and a constant volume of distilled water. Sedentary activity was permitted.

The effects of hydrochlorothiazide and spironolactone (an aldosterone inhibitor), given both alone and in combination, were studied over periods of 4 or 8 days. The results showed a marked loss of potassium by oedematous

patients receiving hydrochlorothiazide. The addition of spironolactone in small doses produced a sodium diuresis with a limited potassium loss. Spironolactone given alone in large doses was effective in producing sodium loss in 2 cases of cirrhosis with ascites and one case of congestive cardiac failure, in both of which conditions secondary aldosteronism may play a large part in the sodium retention.

The effects of medication with prednisolone were also observed. In patients who responded to this drug a fall in urinary aldosterone excretion was followed by a sodium diuresis. *G. S. Crockett*

862. **The Effect of Phenylbutazone (Butazolidin) on Plasma Pepsinogen Activity**
K. D. MUIRDEN. *Gut* [*Gut*] **2**, 40–43, March, 1961. 3 figs., 17 refs.

In order to throw further light on the mechanism of production of such side-effects as epigastric discomfort and nausea which occur in patients receiving phenylbutazone, the plasma pepsinogen activity was measured at intervals in 9 female patients at the Royal Melbourne Hospital, Australia, during treatment with the drug in a dosage of 300 to 400 mg. a day and in a further 6 patients receiving phenylbutazone in the same dosage together with the anticholinergic drug oxyphenonium bromide (" antrenyl ") in a dosage of 5 mg. four times a day.

In all 15 cases the plasma pepsinogen activity (estimated by Mirsky's modification of Ansen's method) rose during treatment with phenylbutazone, the highest level being noted in the first week of treatment with a tendency to fall to pre-treatment levels later. The results were similar in those taking antrenyl in addition. Though the exact relation between peptic cell activity and plasma pepsinogen activity is uncertain, the author considers it possible that the results of this study may reflect damage to the stomach mucosa by phenylbutazone rather than a change in gastric secretory activity. *G. S. Crockett*

863. **The Effect of Repeated Doses of Neuroleptic Drugs on the Blood–Brain Barrier.** (Beeinflussung der Blut-Hirnschranke durch Neuroleptica im Dauerversuch)
G. QUADBECK and W. SACHSSE. *Archiv für Psychiatrie und Nervenkrankheiten* [*Arch. Psychiat. Nervenkr.*] **201**, 580–592, 1961. 1 fig., 16 refs.

In an experimental study carried out at the University of Saarland, Homburg, to determine the effect of repeated doses of neuroleptic drugs on the blood–brain barrier rats were given over a period of 4 weeks 22 treatments of electric convulsion therapy and also three drugs commonly used in the treatment of the endogenous psychoses, namely, chlorpromazine, perphenazine, and reserpine.

It was shown that after this prolonged treatment the permeability of the blood–brain barrier for phosphates was increased and that for sodium diminished. The authors consider that both these effects suggest that these forms of treatment result in an improvement in cerebral nutrition, the improved permeability bringing about a better supply of nutrient material; the reduction in sodium loss indicates a diminished nutritional requirement, since sodium metabolism is an index of cerebral metabolism in general. In the case of chlorpromazine the effect persisted after the drug was withdrawn. They point out that the effect of single doses of these drugs, however, is often quite different from that of repeated doses. *J. Hoenig*

864. **Evaluation of UML–491 in the Treatment of Vascular Headaches: an Analysis of the Effects of 1-Methyl-D-lysergic Acid (+) Butanolamide Bimaleate (Methysergide)**
A. P. FRIEDMAN and S. LOSIN. *Archives of Neurology* [*Arch. Neurol. (Chicago)*] **4**, 241–245, March, 1961. 9 refs.

At Montefiore Hospital, New York, " methysergide " (UML–491; 1-methyl-D-lysergic acid (+) butanolamide bimaleate), a serotonin antagonist, was given as a prophylactic in the management of 150 patients with migraine, and 21 patients with cluster or Horton's headache. The drug was given by mouth in a dosage of 8 mg. daily for 5 days, followed by an average maintenance dosage of 6 mg. daily. There was a reduction in the frequency and severity of headaches in 97 (65%) of the patients with migraine and in 15 (71%) of those with cluster headache, the response in the former group being significantly different from the placebo response. Side-effects, which were severe enough in 17 patients to necessitate cessation of treatment, included giddiness, nausea, epigastric distress, and difficulty in concentration. In one patient generalized cramps and numbness with diminution of the pulses in the limbs developed. The authors recognize that the exact mode or site of action of the drug is unknown, but conclude that further controlled clinical and pharmacological studies are necessary for a final evaluation. *I. Ansell*

865. **The Effect of Certain Psychopharmacologic Agents on Liver and Brain Sulfhydryl Levels**
C. A. BRADLEY, T. S. MIYA, and G. K. W. YIM. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] **2**, 175–177, April, 1961. 12 refs.

This paper from Purdue University, Lafayette, Indiana, describes experiments in which the effect of various psycholytic drugs on the concentration of total non-protein sulphydryl in the liver and brain of rats was investigated, the authors having in mind the possibility that mental disturbances may be produced by biochemical changes involving glutathione and its sulphydryl group. The livers and brains of the animals were removed and examined biochemically after the administration of simple saline, lysergic acid diethylamide (L.S.D.), adrenaline, serotonin, 5-hydroxytryptophan, adrenochrome, and mescaline. The dosages and results are tabulated.

It was found that the gross behavioural changes induced by these chemicals were not necessarily reflected in changes in the liver glutathione levels, that none of the agents used affected the non-protein sulphydryl levels in the brain, and also that changes induced by L.S.D. were not relieved by the injection of glutathione. *B. M. Davies*

Chemotherapy

866. **Triacetyloleandomycin—a Substitute for Penicillin G. A Comparison of the Therapeutic Effectiveness of Triacetyloleandomycin, Erythromycin Propionate, and Oral Penicillin G in the Treatment of Beta Hemolytic Streptococcal Infections**

B. B. Breese, F. A. Disney, and W. B. Talpey. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] 101, 423–428, April, 1961. 1 fig., 12 refs.

Three antibiotics, triacetyloleandomycin ("cyclamycin"), erythromycin propionate ("ilosone"), and penicillin G were tested as therapeutic agents in the treatment of streptococcal infection in children. Although all 3 were equally and rapidly effective in controlling the disease initially, recurrences and carriers occurred more frequently and earlier after the conclusion of therapy with the erythromycin propionate than with triacetyloleandomycin or penicillin. When followed up over a 2-month period, the number of carriers or recurrences observed after penicillin was higher than after the use of triacetyloleandomycin. However, when the observations were limited to one month after the conclusion of therapy, no significant difference was observed. Acceptance of the drug by the patients was good, and side-reactions with all 3 drugs were minimal.

It is concluded that triacetyloleandomycin is at least as effective as oral penicillin in the treatment of β-hemolytic streptococcal infections in children, and superior to erythromycin propionate.—[Authors' summary.]

867. **Nitrogen Mustard in Palliation of Malignant Effusions**

V. B. Levison. *British Medical Journal* [*Brit. med. J.*] 1, 1143–1145, April 22, 1961. 15 refs.

An investigation was carried out at the North Middlesex Hospital, London, into the value of treating recurrent malignant effusion by the intracavitary injection of mustine hydrochloride (nitrogen mustard). Nineteen patients, all of whom had carcinoma (6 of the bronchus, 4 of the alimentary tract, 2 of the breast, and 7 of the female genital tract) with recurrent pleural effusion, ascites, or both received treatment. Paracentesis preceded treatment and the patient was given 50 mg. of chlorpromazine intramuscularly 30 minutes before the injection. The dose of mustine hydrochloride was 10 to 30 mg. (average 20 mg.) in 20 ml. of sterile saline. The patient was moved frequently during the 2 hours after this injection to distribute the solution evenly. No further paracenteses were carried out until further symptoms developed.

Eight patients showed no improvement and in 3 the fluid formation continued, but in decreasing amounts. In 6 of the remaining 8 no further paracentesis was necessary until the time of death (2 to 15 months); of the other 2 patients, one lived 9 months and required paracentesis twice and one lived 27 months and required tapping only once during this time. The 11 patients who responded to treatment included 4 with ovarian adenocarcinoma and 4 with bronchial carcinoma, both patients with carcinoma of the breast, and one with carcinoma of the stomach. Three patients with effusions due to metastasis from gastro-intestinal carcinoma showed no improvement. Many patients had transient nausea and vomiting and this persisted for 48 hours in 2 cases and 72 hours in one. Two patients had transient pyrexia, and local irritation occurred in one case. Blood counts after treatment were all normal.

Anne Tothill

868. **Role of Cytotoxic Agents in Production of Amyloidosis in Hodgkin's Disease**

B. S. Cardell. *British Medical Journal* [*Brit. med. J.*] 1, 1145–1148, April 22, 1961. 14 refs.

From King's College Hospital Medical School, London, 4 cases are reported in which amyloidosis developed after treatment with mustine hydrochloride (nitrogen mustard) or tretamine (triethylenemelamine). In a series of 3,192 consecutive necropsies performed between 1947 and 1959 20 cases of amyloidosis occurred, in 6 of which the disease was primary; of the remainder, it was associated with Hodgkin's disease in 4 cases, multiple myelomatosis in 3, pulmonary tuberculosis in 3, rheumatoid arthritis in 2, osteomyelitis in one, and empyema in one. All of the 4 patients with Hodgkin's disease had been treated with either mustine hydrochloride or tretamine. Altogether there were 22 patients with Hodgkin's disease in this series, of whom 14 had no amyloidosis and had had no cytotoxic drugs and 4 had received cytotoxic drugs but had no amyloidosis.

In the first of the 4 cases of amyloidosis a woman aged 25 received 2 courses of mustine hydrochloride, one of 18 mg. and the other of 21·6 mg., at an interval of 5 months. Proteinuria and gross oedema developed 10 months after the final treatment and she died at this time. In the second case a man of 22 received 10 mg. of tretamine intravenously. He developed proteinuria after one month and died within 2 weeks. In the third case a woman of 39 received 10 mg. of tretamine. Two months later she had ankle oedema and moderate proteinuria and she died within a month. In the fourth case a man of 65 was given 18·9 mg., 15 mg., and 15 mg. of mustine hydrochloride in 3 separate courses at 6-month intervals over a period of one year. Ankle oedema developed 5 months after the second course of treatment and he died a week after the third course. At necropsy extensive amyloidosis associated with Hodgkin's disease was found in all these patients. The author suggests that cytotoxic drugs do not initiate amyloidosis, but accelerate a process that is already taking place.

Anne Tothill

Infectious Diseases

869. **Effect of Sabin Type 1 Poliomyelitis Vaccine Administered by Mouth to Newborn Infants**
M. L. LEPOW, R. J. WARREN, N. GRAY, V. G. INGRAM, and F. C. ROBBINS. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 1071–1078, May 25, 1961. 5 figs., 26 refs.

From the Western Reserve University School of Medicine and the Metropolitan General and University Hospitals, Cleveland, Ohio, the authors describe the responses of 144 newborn infants to the feeding within 24 hours of birth of 1 ml. of Type-1 attenuated poliovirus vaccine (Sabin LSc–2 ab) containing $10^{7.5}$ $TCID_{50}$ (Group 1) and compare them with those of 70 infants fed approximately one-thirtieth of the amount of the same vaccine at 3 months of age (Group 2). Only 9 of the mothers lacked detectable antibody to Type-1 virus.

No illnesses that could be attributed to the vaccine occurred amongst the vaccinated infants and no contact infants acquired infection. In Group 1 Type-1 poliovirus was recovered from the faeces at some time during the first 2 weeks after feeding in 81% of cases and in Group 2 in 93% of cases. At 6 weeks after feeding, 15% of Group 1 and 30% of Group 2 were still excretors. In Group 1 excretion was still found in 5 cases at 10 weeks and in one at 16 weeks. High titres of virus in the faeces were significantly more frequent in Group 2 than in Group 1.

Active antibody response was determined in both groups by comparing the serum neutralizing antibody titre before vaccination with that at 7 months of age; to be of significance the titre at 7 months had to exceed at least 8-fold that to be expected if the half-life of passively acquired antibody were 45 days. By this criterion, approximately 50% of Group 1 developed active immunity compared with 93% of Group 2. Almost all the babies who failed to develop active immunity or who did not become infected had had maternal antibody titres of 128 or greater at birth. Of the 42 in Group 1 with low passive antibody titres, 98% excreted virus and 83% developed antibodies. High passive antibody titres appeared not only to suppress infection of the gastrointestinal tract, but also to inhibit active immune response even in the face of established infection of the bowel. Breast feeding influenced the response of neonates adversely when the maternal antibody titre was high. No difficulties were encountered from interfering wild enteroviruses, and inactivation of virus in the stomach did not appear to be a problem. *A. Ackroyd*

870. **Measles Encephalitis. Evaluation of Treatment with Adrenocorticotropin and Adrenal Corticosteroids**
S. KARELITZ and M. EISENBERG. *Pediatrics* [*Pediatrics*] **27**, 811–818, May, 1961. 14 refs.

The authors describe the course and treatment of 42 patients, 23 male and 19 female, admitted with measles encephalitis to the Queens General Hospital and the Long Island Jewish Hospital, New York, between 1952 and 1959, of whom 20 were followed up 2 to 7 years after discharge. The patients' ages ranged from 1 to 35 years, but the majority (30) were aged between 5 and 9 years. All but 3 were admitted within 24 hours of the onset of cerebral symptoms, at which time 23 patients were comatose, 15 lethargic, and 30 were having convulsions. In 41 cases the encephalitis became manifest 1 to 7 days after the measles rash appeared, in the majority (27 cases) on the 3rd, 4th, or 5th day; no case occurred in the incubation or pre-eruptive period. The time of maximum prevalence of measles was between March and June in the New York area.

Examination of the cerebrospinal fluid (C.S.F.) revealed wide variations. Thus the cell count ranged from below 20 to 650 per c.mm., lymphocytes predominating [numbers not given], the protein content ranged between 50 and 197 mg. per 100 ml., and the sugar content from 48 to 197 mg. per 100 ml. The leucocyte count in the peripheral blood also varied widely, ranging from less than 10,000 to over 20,000 per c.mm., while differential count showed polymorphonuclear cells in the range of 40 to 93%. The electroencephalogram was recorded on the 4th to the 30th day of illness in 19 cases and revealed abnormalities in 17. No attempt was made to isolate measles virus from the C.S.F.

Treatment was as follows. In 32 cases penicillin was given daily and 6 of these received chloramphenicol and 5 tetracycline in addition [doses not given], while in 28 cases the patient was placed in an oxygen tent. Intravenous fluids were given for the correction of electrolyte imbalance. Tracheotomy was performed in 2 cases because of excessive secretions, and 3 patients received gamma globulin (12 to 48 ml.). Adrenocortical extract (4 to 12 ml.) was given to 3 patients, 6 received daily doses of ACTH (from 40 units diminishing to 5 units) and cortisone (300 mg. gradually reduced to 75 mg.), while "several others" received the corticosteroids. Convulsions were treated by intravenous administration of barbiturates. All the patients survived. Emergence from coma or lethargy and cessation of convulsions occurred in most cases 24 to 72 hours after admission. Of 13 patients discharged with sequelae, 9 of whom had received steroids or ACTH, 3 developed behaviour defects, 3 mental deterioration, one schizophrenia and epilepsy, one muscular spasticity, and one paresis of the extremities. Of the 4 not given steroids, 3 manifested behaviour disturbances and one mental deterioration. Follow-up examinations carried out up to 7 years later showed that of 14 patients treated with ACTH and/or steroids, only 2 were completely well, 12 showing sequelae (7 emotional disturbance, 3 epilepsy, and one paresis of the lower extremities, which, however, was less severe than on discharge 2 years earlier).

The authors conclude that the use of ACTH and cortisone did not prevent neurological complications and possibly exaggerated them when present. They

therefore do not advise these agents in the treatment of measles encephalitis and suggest that the prompt institution of the supportive regimen described above was the chief factor in the survival of all 42 of their patients.

[This paper is not clearly presented, but is nevertheless valuable in that it once again demonstrates the dangers as well as the uselessness of steroids in viral infections.]

I. M. Librach

871. **Bornholm Disease Survey 1956, 1957 and 1958**

W. O. WILLIAMS. *Journal of the College of General Practitioners* [*J. Coll. gen. Practit.*] **4**, 181–213, May, 1961. 6 figs., 33 refs.

In the summer of 1956 an outbreak of over 2,000 cases of Bornholm disease occurred in Swansea, South Wales. In view of this large outbreak an attempt was made to study the extent of the disease not only in South Wales, but throughout the British Isles in that year and also by questionary in the years 1957 and 1958. Eventually a total of 186 cases with sufficient clinical details were collected. This series consisted of 87 males and 99 females ranging in age from under 1 year to 70 years. The disease showed the greatest prevalence and the highest attack rate among those under 15 years of age. The onset of the illness was usually abrupt, while its duration varied from 1 to 40 days, being in 52·7% of cases, however, from 1 to 5 days. The most prominent symptom, present in every case, was myalgia, which in 86 cases was characteristically costo-diaphragmatic in distribution. Other common symptoms included, in order of frequency, intermittent fever, profuse sweating, frontal headache, anorexia, nausea, sore throat, vomiting, and rigors. It is noted that of 46 patients showing oedema of the soft palate with reddening of the palatopharyngeal mucosa, only 16 complained of a sore throat. Few physical signs were helpful in the diagnosis. There were relatively few complications; 3 patients who were in the 12th, 30th, and 38th weeks of pregnancy respectively when they developed the disease all gave birth to normal babies, and no cases of orchitis, lymphocytic meningitis, abortion, pericarditis, or encephalitis were observed. The most interesting complication (one case) was paroxysmal tachycardia in a girl aged 7 years who continued to have attacks for 18 months.

It is suggested that although the Coxsackie Group B virus is an enteric virus, it may enter the body through the nasopharynx and only later appear in the bowel. Investigations in this study showed that the virus is excreted in the faeces for at least a week and in some cases up to 3 weeks after clinical recovery. Among the interesting physical signs were (1) thoracic friction rub (7 cases), which the author considers may be either of muscular origin or a friction rub between the parietal pleura and the chest wall; (2) reddening of the conjunctivae, which occurred most frequently in patients who suffered from profuse sweating; and (3) a grunting type of respiration, an important characteristic of the disease and exhibited by 27 patients, most of whom were under 5 years of age. The highest seasonal incidence of Bornholm disease was in the warmer months of the year (June and July). Close personal contact was found to be an important factor in the spread of infection. The incubation period was 3 to 7 days, and the serial interval varied from less than 24 hours to 33 days. The density of infection in Swansea was sparse (one case per house) in the majority (38) of the 51 affected households. There was no evidence of spread of the infection by milk in South Wales. The absence of poliomyelitis in Swansea during the 1956 epidemic of Bornholm disease may possibly be attributed to interference with the virus of this disease by the Coxsackie virus. In no case was Coxsackie virus Type B5, which is known to cause aseptic meningitis, isolated from patients with Bornholm disease and no case of meningitis occurred.

R. G. Meyer

872. **Chickenpox and Leukemia**

D. PINKEL. *Journal of Pediatrics* [*J. Pediat.*] **58**, 729–737, May, 1961. 4 figs., 25 refs.

Chickenpox occurring in patients suffering from acute leukaemia runs a severe and often fatal course and this report from Roswell Park Memorial Institute and the University of Buffalo School of Medicine, Buffalo, New York, deals with 4 such cases. Death occurred in 2 of these from the chickenpox infection itself, whereas in the other 2 administration of γ globulin appeared to help to control the infection, although both patients died later from leukaemia. Necropsy in the first 2 cases revealed focal hepatic necrosis with pulmonary haemorrhages and oedema. A noticeable feature was the lack of inflammatory response, suggesting a deficiency of cellular reaction to the infection. The serious course of chickenpox in these patients may have been due to the leukaemia itself, with a possible deficiency in cellular immunity, or to the drugs given, adrenal steroids, 6-mercaptopurine, and amethopterin, all of which are known to inhibit immune responses to certain infections.

Winston Turner

873. **Neonatal Tetanus in Sierra Leone**

J. L. WILKINSON. *British Medical Journal* [*Brit. med. J.*] **1**, 1721–1724, June 17, 1961. 19 refs.

An analysis is presented of 114 consecutive cases of neonatal tetanus treated at the Nixon Memorial Hospital, Segbwema, Sierra Leone, over a period of 5½ years. The rather primitive ecological background is described with particular reference to the native's method of tying the umbilical cord and care of the cord after birth. Most of the cases were severe and occurred during the wet season. The average age on admission of those infants who survived was 10·5 days, whereas for those who died it was 6·3 days. The initial symptoms were trismus with inability to suck followed by muscle rigidity and severe spasms. A single dose of 10,000 units of antitetanus serum and injections of penicillin were given to all patients. Chlorpromazine in a dosage of 10 mg. every 4 hours and later 6-hourly and 8-hourly was given intramuscularly to 70 of the infants, of whom 34 (48·6%) died. Of 44 infants treated earlier with sedation and (in 24 of them) with mephenesin, 32 (72·7%) died. The authors emphasize the danger of overdosage of chlorpromazine; they consider that the optimum dosage is 4·5 mg. per kg. body weight daily initially, reduced to 2·3 mg. per kg. later.

Winston Turner

Tuberculosis

874. **Influence of Segregation of Tuberculous Patients for One Year on the Attack Rate of Tuberculosis in a 2-Year Period in Close Family Contacts in South India**
C. V. RAMAKRISHNAN, R. H. ANDREWS, S. DEVADATTA, W. FOX, S. RADHAKRISHNA, P. R. SOMASUNDARAM, and S. VELU. *Bulletin of the World Health Organization* [*Bull. Wld Hlth Org.*] **24**, 129–148, 1961. 3 figs., 5 refs.

An investigation has been conducted at the Tuberculosis Chemotherapy Centre, Madras, into the attack rate among family contacts during the 2 years after the beginning of chemotherapy of tuberculous patients living in an overcrowded urban community. The present report deals with the 256 contacts of 75 patients treated at home and 274 contacts of 73 patients treated in a sanatorium. Radiographic examination of contacts was carried out periodically during the 2 years, with a coverage of 94%.

During the first year active tuberculosis developed in 27 contacts (9 "home" and 18 "sanatorium" contacts), and 7 further cases (3 "home" and 4 "sanatorium" contacts) were discovered in the 2nd year. Of the 34 cases in which tuberculosis developed, this was within the first 3 months in 18, and these cases have been attributed to infection by the index case before the start of treatment. The 7 cases in which tuberculosis developed in the 2nd year had all been initially tuberculin-positive. Of the total 34 patients, 17 were under 5 years of age and 24 under 10. Serial tuberculin tests during the 2 years did not show any evidence of more severe tuberculous infection in contacts of patients treated at home than in those of patients treated in a sanatorium. The attack rate in contacts of home-treated patients was no greater than in those of patients segregated in a sanatorium. It is concluded that the major risk to contacts was exposure to the index case before diagnosis.

G. M. Little

875. **Progress in the Second and Third Years of Patients with Quiescent Pulmonary Tuberculosis after a Year of Chemotherapy at Home or in Sanatorium, and Influence of Further Chemotherapy on the Relapse Rate**
S. DEVADATTA, R. H. ANDREWS, J. H. ANGEL, A. L. BHATIA, W. FOX, B. JANARDHANAM, S. RADHAKRISHNA, C. V. RAMAKRISHNAN, T. V. SUBBAIAH, and S. VELU. *Bulletin of the World Health Organization* [*Bull. Wld Hlth Org.*] **24**, 149–175, 1961. 1 fig., 25 refs.

This is the report of a follow-up study at 2 to 3 years of the patients taking part in a controlled comparison between domiciliary and sanatorium treatment organized by the Tuberculosis Chemotherapy Centre, Madras. The study covers 126 patients who had been treated with PAS and isoniazid for a year and whose disease had become quiescent in that time. During the 2nd year 65 of the 126 were given isoniazid in doses of 150 to 200 mg. daily and 61 were given tablets of calcium gluconate, 500 mg. daily. In the 3rd year 30 of the patients treated with isoniazid continued on this drug and 30 others were given calcium gluconate, while those already receiving calcium gluconate were given this drug for a further year. All patients were treated at home during the 2nd and 3rd years.

Of the 61 patients who received only one year of chemotherapy, 6 (10%) relapsed bacteriologically compared with 3 (5%) of 65 who received 2 or 3 years of chemotherapy. Of 57 patients treated at home in the first year, 3 (5%) relapsed compared with 6 (9%) of 69 treated in a sanatorium during that time. Of the 42 patients with a cavity but no positive sputum at the end of a year, 4 (10%) relapsed compared with 5 (6%) of the 84 patients who had no cavitation. Of the 9 cases which relapsed during the period of the trial, 8 did so during the 2nd year.

The authors consider that in the 2nd and 3rd years there was relatively little difference between the patients who had domiciliary treatment and those who were treated in a sanatorium. Treatment with isoniazid alone during the 2nd and 3rd years gave no better results than one year of chemotherapy followed by observation of the patient and further chemotherapy if a relapse occurred. Patients with residual cavitation at the end of a year of chemotherapy showed a slightly higher relapse rate than those with no cavitation.

G. M. Little

876. **Initial Chemotherapy in Pulmonary Tuberculosis: Daily Streptomycin with High Isoniazid Dosage in Previously Untreated Cases.** [In English]
A. SALIBA, L. PACINI, C. W. DOWDEN, and O. A. BEATTY. *Acta tuberculosea Scandinavica* [*Acta tuberc. scand.*] **40**, 113–125, 1961. 9 figs., 18 refs.

The authors, writing from District Two State Tuberculosis Hospital, Louisville, Kentucky, point out that there is but scant literature on the combination of daily streptomycin and high doses of isoniazid in the treatment of tuberculosis. Their justification for a high isoniazid dosage is that variable and sometimes ineffectual blood levels of isoniazid are occasionally found when conventional dosage is given.

Patients were accepted for the trial here described if they had pulmonary tuberculosis proved by sputum culture and previously untreated by antituberculous drugs or if they had been treated for less than 3 months and were excreting organisms sensitive to streptomycin and isoniazid. Two groups were established, but were not comparable. The majority of patients were white and aged between 18 and 39 years; and almost all in both groups had cavitated disease. Strict rest in bed was not enforced. Group I consisted of 42 patients (with more extensive disease than those in Group II) who were given daily 16 mg. of isoniazid per kg. body weight, together with 50 to 100 mg. pyridoxine and 1 g. streptomycin. The average duration of administration of streptomycin

was 4 months, after which it was replaced by PAS, 8 to 12 g. daily. Group II, consisting of 15 patients, were given isoniazid, 300 mg. daily, and streptomycin, 1 g. daily for 90 days.

In Group I only 3 patients had positive sputum after one to 3 months, and this became negative in 4 to 6 months, while in Group II only one had positive sputum after one to 3 months, becoming negative in 4 to 6 months. Radiological improvement in both groups was less impressive than sputum conversion. "Significant vestibular dysfunction" was found in 3 cases and some degree of deafness discovered by audiometry in 2, though the patients did not complain. Skin reactions in 2 cases responded to treatment without the drugs being stopped. No other incommoding toxicity was observed.

The authors are of the opinion that daily streptomycin and high dosage of isoniazid are indicated in new and untreated cases of tuberculosis and that side-effects are not severe or frequent enough to invalidate it. But if adequate blood levels of isoniazid can be shown with conventional doses, then high dosage is not necessary. [Blood levels were not determined in their cases.]

[The work covered initial antituberculous therapy in 2 small, non-comparable groups, and it cannot be said to have verified the claim for the therapeutic value of high dosage of isoniazid.] *W. Raymond Parkes*

877. **Initial Treatment of Pulmonary Tuberculosis with Isoniazid in Association with Ethionamide.** (Traitement d'attaque de la tuberculose pulmonaire commune par l'association d'isoniazide et d'éthioniamide)
G. Brouet, J. Marche, J. Chevallier, M. H. Nicolle, and P. Névot. *Revue de Tuberculose et de Pneumologie* [*Rev. Tuberc.* (*Paris*)] **25**, 145–190, Feb.–March [received June], 1961. 1 fig., bibliography.

The authors describe the results of treatment in 66 patients (51 male) with pulmonary tuberculosis, of whom 53 had recent, untreated, disease and 13 had recurrence after at least 2 years of disease previously considered to be cured. They were all given for at least 3 months isoniazid, 10 mg. per kg. body weight, together with ethionamide, 250 mg. three or four times a day, and were then followed up clinically, radiologically, and bacteriologically. From the patient's point of view and also radiologically the results were considered satisfactory. Bacteriologically, the sputum had become negative in 48 (90%) of the new cases by the end of the third month and in 10 (80%) of the recurrent cases.

Unfortunately ethionamide causes considerable gastric upset and in only 30% of the cases were gastric symptoms absent. Anorexia was the commonest complaint. Some of the patients developed a depressive state with suicidal tendencies, while seborrhoeic dermatitis, acne, and neurotoxic manifestations were other complications. There is little doubt that some of these toxic phenomena are due to nicotinamide deficiency and can be prevented or alleviated by the administration of this member of the vitamin-B complex. The authors point out that in patients suffering from general malnutrition or psychic trouble the combination of isoniazid and ethionamide has to be used with considerable care.

[The dosage of isoniazid was high and some of the toxic symptoms might have been attributable to this drug.] *Paul B. Woolley*

878. **Streptomycin plus Pyrazinamide in the Treatment of Patients Excreting Isoniazid-resistant Tubercle Bacilli, following Previous Chemotherapy**
S. Velu, R. H. Andrews, J. H. Angel, S. Devadatta, W. Fox, P. G. Jacob, C. N. Nair, and C. V. Ramakrishnan. *Tubercle* [*Tubercle* (*Lond.*)] **42**, 136–147, 1961. 22 refs.

Up to August 31, 1959, a total of 69 patients with chronic pulmonary tuberculosis had been treated at the Tuberculosis Chemotherapy Centre, Madras, with streptomycin together with pyrazinamide. In all cases the sputum contained bacilli which were sensitive to streptomycin but resistant to isoniazid. Of the 69 patients, 12 were excluded from the analysis for various reasons; of the 57 with whom this report is concerned (30 males and 27 females aged 17 to 64 years), 30 had been treated previously with PAS and isoniazid, without improvement in 22 and with temporary improvement followed by relapse in 8. The remaining 27 patients had been given isoniazid alone, but without improvement.

In the present trial the patients received intramuscular injections of streptomycin in a dosage of 1 g. daily for 6 days in the week and pyrazinamide, 1 to 1·5 g. daily. The dosage of streptomycin had to be reduced in 15 patients to 15 mg. per kg. body weight because of giddiness. Most of the patients had advanced disease and were treated as out-patients, continuing their usual activities. The treatment was given for a year unless at 6 months bacilli resistant to streptomycin were cultured from the sputum, when the treatment was changed, experience having shown that this regimen was unlikely to be effective. The authors state that considerable difficulty was experienced at the Centre with sensitivity tests for pyrazinamide and no reliable results were obtained.

At the end of one year radiological examination showed improvement in 30 patients, no change in 4, and deterioration in 2; the treatment had been changed in 20 and one patient had died. The sputum was negative at one year in 32 patients and positive in 23; in one case the results of culture were doubtful. It was noted that in the early months of treatment bacteria disappeared quickly from the sputum, but in patients who were later to become streptomycin-resistant bacteria rapidly reappeared; this "fall and rise" phenomenon, which was characteristic, permitted recognition of the failures usually at the end of 6 months. Unfavourable prognostic signs were severe disease, extensive cavitation, and an initial heavy growth of bacteria. Giddiness was a common toxic effect of streptomycin; pyrazinamide caused no signs of liver disease, but in 14 patients polyarthritis developed. The treatment was continued during pregnancy in 7 patients without ill-effect.

The authors consider that streptomycin with pyrazinamide is a useful form of treatment for tuberculosis when PAS and isoniazid have failed.

Arthur Willcox

879. **The Treatment of Pulmonary Tuberculosis with Isoniazid and Sulfadimethoxine: a Controlled Study**
W. WEISS, HING HUA CHUN, and H. F. FLIPPIN. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **241**, 448–453, April, 1961. 1 fig., 9 refs.

The sulphonamides have for some time been known to have tuberculostatic properties, but their use in active tuberculosis has given rise to conflicting reports. Studies *in vitro* having shown sulphadimethoxine (" madribon ") to be antagonistic to tubercle bacilli, the authors have carried out a clinical trial at Philadelphia (Pennsylvania) General Hospital to compare the therapeutic efficacy of isoniazid–sulphadimethoxine with that of isoniazid–PAS in advanced, previously untreated pulmonary tuberculosis. The results obtained with the former combination were poor compared with those with the latter. It is concluded that the " companion " drug to isoniazid must have some therapeutic contribution of its own to make and that it must also prevent the emergence of resistance to isoniazid.

[These results are in agreement with majority opinion in Britain—that the sulphonamides are of little value in pulmonary tuberculosis.] *Paul B. Woolley*

880. **Bacteriological Examination of Laryngeal Mucus and of Bronchial and Stomach Washings in Abacillary Patients with Pulmonary Tuberculosis.** (Бактериоскопический метод исследования гортанной слизи, промывных вод бронхов и желудка у абациллярных больных легочным туберкулезом)
A. I. EFIMOVA. *Советская Медицина* [*Sovetsk. Med.*] **25**, 117–121, May, 1961. 18 refs.

This investigation was carried out on 150 patients suffering from pulmonary tuberculosis but whose sputum was negative for tubercle bacilli. In 48 (32%) of these cases bacteriological examination of the laryngeal mucus or of the washings after lavage of the bronchi or stomach revealed the presence of the causative organisms. The individual proportions of positive findings in the three possible sources of tubercle bacilli were 11·3% for the laryngeal mucus, 17·4% for the bronchial washings, and 17·3% for the gastric washings. *A. Orley*

881. **Relapse in Pulmonary Tuberculosis: an Analysis of the Fate of Patients Notified in 1947, 1951 and 1954**
A BRITISH TUBERCULOSIS ASSOCIATION REPORT FROM THE ASSOCIATION'S RESEARCH COMMITTEE. *Tubercle* [*Tubercle (Lond.)*] **42**, 178–186, 1961. 1 fig.

A retrospective survey is reported of the relapse rate in quiescent pulmonary tuberculosis, based on a random sample of cases notified at 15 centres in England and Scotland in the years 1947 (before the introduction of chemotherapy), 1951 (when chemotherapy was imperfectly used), and 1954 (when treatment was good). The disease was considered quiescent when no symptoms of toxicity were noted and cultures were negative on 3 consecutive occasions or sputum was absent. The disease was considered to have relapsed: (1) when sputum became positive after being negative for more than 3 months from the day quiescence was achieved (one positive result was sufficient evidence of relapse provided it was acted upon, while two positive results were sufficient evidence if occurring within 6 months of each other, even if no action was taken at the time); and (2) when there was radiological evidence of deterioration attributable to tuberculosis. Complications due to cor pulmonale, chronic bronchitis, and emphysema were not classified as relapses. Of 2,269 patients in the survey originally, 406 (17·9%) were untraced. The remainder were classified as follows:

Year	No. of Patients	Never Quiescent	Quiescent
1947	311	140 (45%)	171
1951	571	116 (20·3%)	455
1954	981	106 (10·8%)	875
Total	1,863	362 (19·4%)	1,501

The relapse rate per annum in patients notified as suffering from tuberculosis in 1947 was fairly high for the first 5 years and then declined, but relapses were still occurring even after periods of quiescence of 8 years and more. The relapse rate in the 1951 group was even higher for the first 4 years and then declined; this, it is suggested, was probably due to the fact that some of these patients would have died but for chemotherapy, which, however, was not well administered and relapse followed its withdrawal. The relapse rate in the 1954 group was lower than in either of the other two groups. Relapses were commoner in males than in females, particularly in patients over 45 years of age. The extent of the disease had some influence, the relapse rate for all years combined increasing from 15·4% in cases of minimal disease to 19·7% in cases of far-advanced disease. The difference in relapse rate was most marked in the 1951 group (minimal disease 20·4%, far-advanced disease 38·1%). In the 1954 group, however, the relapse rate was higher in cases of minimal disease (11·4%) than in cases of far-advanced disease (7·9%). This is attributed to the fact that " a proportion of minimal cases received no specific treatment or received short courses only ". A similar anomaly was observed when cases showing cavitation were analysed. In 1954 the relapse rate in patients without cavitation was 9·7% compared with 6·4% in those with cavities; however, only 76% of the patients without cavitation had received chemotherapy, whereas it had been given to 96·8% of those with cavities. The extent of the disease and cavitation thus appeared to be less reliable guides to prognosis than the intensity and duration of chemotherapy. In all groups the relapse rate was higher in patients with a positive sputum (19·3%) than in those with a negative sputum (13·6%). Resection with chemotherapy and permanent collapse measures combined with chemotherapy were associated with a low relapse rate. Temporary collapse therapy alone was followed by a high relapse rate.

Finally, the importance is emphasized of careful follow-up of patients notified as suffering from tuberculosis in 1947, since relapses still occur, and of those notified in 1951 who may relapse and, because of poor chemotherapy, may still have drug-resistant tubercle bacilli in the sputum. *Arthur Willcox*

Venereal Diseases

882. **Incidence of Urethral Stricture in the Male after Urethritis**

E. M. C. DUNLOP. *British Journal of Venereal Diseases* [*Brit. J. vener. Dis.*] **37**, 64–69, March, 1961. 4 refs.

The author reports a study of the incidence of urethral stricture in the male after treatment by modern methods for gonococcal or non-gonococcal urethritis. Four weeks or more after the infection had apparently responded to treatment instrumental examination was carried out on 498 out of 1,244 male patients attending 4 clinics. In 23 cases (4·6%) a urethral stricture was found. Five of these were meatal (in 3 cases probably due to balanitis xerotica obliterans), 2 were intrameatal, 5 were in the shaft of the penis, and 11 were in the region of the bulb. Sixteen occurred among 328 cases of non-gonococcal urethritis (4·9%), 2 among 113 cases of gonorrhoea (1·8%), and 5 among 57 cases of urethritis in which treatment had been given previously elsewhere and of which the aetiology was therefore unknown (9%). The incidence of stricture was similar in white and coloured patients. *R. R. Willcox*

SYPHILIS

883. **The Treponemal Immobilization (Nelson) Test in Congenital Syphilis.** (Le test d'immobilisation des tréponèmes pâles (test de Nelson) dans la syphilis congénitale)

J. DELACRETAZ. *Archives belges de dermatologie et de syphiligraphie* [*Arch. belges Derm.*] **16**, 333–339, Dec., 1960 [received May, 1961]. 10 refs.

The author, writing from the University Clinic of Dermato-Venereology, Lausanne, points out that a definite diagnosis of congenital syphilis is difficult when the clinical signs in the newborn infant, the results of standard serological tests for syphilis (S.T.S.), and the parental case history are not in agreement. The present study was designed to assess the value of the treponemal immobilization (T.P.I.) test in 51 cases (which are tabulated and briefly summarized) in which such disagreement existed. The test did not give a clear lead as to how to interpret the conflicting data, for in apparently identical circumstances it gave different results. In a further study the sera from 24 cases of treated congenital syphilis were subjected to S.T.S. and the T.P.I. test. In 22 of these the latter gave a positive result, whereas the S.T.S. were positive in 12, negative in 7, and " dissociated " in 3. In one of the 2 remaining cases the T.P.I. test gradually became negative 20 years after 5 courses of treatment, while in the other it first was negative, then gave a doubtful response (38% immobilization), and finally became negative without further treatment.

In the discussion a case is described in which positive results by both S.T.S. and the T.P.I. test were obtained with the cord blood at birth and again 18 days later in a newborn infant. Two months later, however, after 3 mega units of penicillin had been given, all the reactions were negative. The author suggests that most probably the positive reactions in this case were due to transplacentally transmitted antibodies, so that a positive result in the T.P.I. test need not necessarily imply congenital syphilis. On the other hand transplacental infection late in pregnancy may produce a negative T.P.I. response soon after birth, but later a positive response during the first year of life. Alternatively, as in a further case described, the antibody titre may be too low to give a positive test; in this case " reactivation " by means of a dose of penicillin then produced a transitory positive T.P.I. test result.

It is concluded that in congenital syphilis a persistently negative response in the T.P.I. test is in favour of cure, but a positive test does not necessarily mean persistent infection. *F. Hillman*

884. **Fluorescent Treponemal Antibody Test Using the Reiter Treponeme**

S. V. COVERT, J. F. KENT, and R. W. STEVENS. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol. (N.Y.)*] **106**, 729–731, April [received June], 1961. 8 refs.

The antigen used in the fluorescent treponemal antibody test described by Deacon *et al.* (*Proc. Soc. exp. Biol. (N.Y.)*, 1957, **96**, 477; *Abstr. Wld Med.*, 1958, **24**, 26) must be a suspension of the virulent Nichols strain of *Treponema pallidum*. This paper from the New York State Department of Health, Albany, describes the results given by the same technique but using a suspension of the easily cultivable Reiter treponeme as antigen. The organisms were grown in thioglycollate broth with 10% heated rabbit serum, cultures being suitable for use from the 2nd to the 5th day after inoculation. When ready, 2 ml. of the undisturbed upper layer of the culture was added to 2 ml. of 0·002% sodium hypochlorite in saline, centrifuged after gentle mixing, washed in saline, and resuspended in enough saline solution to give a density of 10 to 15 treponemes per high dry microscopical field. This procedure prevented clumping of the organisms and changes in their morphology. The technique in all other respects followed Deacon's except that the sera were tested at a dilution of 1 in 200.

Parallel tests performed with the Reiter and the Nichols strains of *T. pallidum* as antigen showed that sera from 103 healthy persons gave negative results with both antigens. A second group of 38 sera tested came from patients with non-treponemal conditions, 35 of whose sera had given positive reactions with cardiolipin antigens; these responses were thought to be non-specific because all the patients gave a negative response in the treponemal immobilization test. In this group the

fluorescent test with Nichols treponemes was negative in all cases, but that using Reiter organisms was positive in one. Quantitative tests on sera from 51 syphilitic patients showed that the Reiter antigen gave a titre double that obtained with the Nichols antigen in 16 instances, while it was half as high in 5 sera, the titres being approximately the same in the remaining patients. This suggests that the Reiter treponeme is slightly though significantly more sensitive as an antigen for detecting syphilitic antibody.

The authors consider that, although further evaluation will be necessary, the Reiter treponeme (which is easily cultivated *in vitro*) may be a possible substitute for the virulent Nichols organism (which can only be cultivated *in vivo*) in the fluorescent treponemal antibody test and that this would facilitate the use of the test in diagnostic laboratories. *A. E. Wilkinson*

885. **Fluorescent Treponemal Antibody Test: a Preliminary Report**
A. E. WILKINSON. *British Journal of Venereal Diseases* [*Brit. J. vener. Dis.*] **37**, 59–63, March, 1961. 15 refs.

The author reports from the London Hospital that of 12 sera from cases of untreated early syphilis (7 of which were of primary syphilis), the fluorescent treponemal antibody (F.T.A.) test of Deacon *et al.* (*Proc. Soc. exp. Biol.* (*N.Y.*), 1957, **96**, 477; *Abstr. Wld Med.*, 1958, **24**, 26) was reactive in 11, the Reiter protein complement fixation (R.P.C.F.) test in 10, and the standard serological tests for syphilis (S.T.S.) also in 10. For 15 sera from treated cases of early syphilis the figures with the three tests were 6, 4, and 3 respectively. In 92 cases of latent syphilis (or yaws) the F.T.A. test produced 86, the R.P.C.F. test 58, and the S.T.S. 73 reactive results, while with sera from 41 cases of late symptomatic syphilis reactive results were obtained in 35, 26, and 33 cases respectively. The F.T.A. test was also used on 144 problem sera. Of 58 which were positive to the treponemal immobilization (T.P.I.) test, 41 were reactive to the F.T.A. test compared with 24 to the R.P.C.F. test and 49 to the S.T.S. Of 86 sera which were negative to the T.P.I. test, only 2 were reactive to the F.T.A. test compared with 8 to the R.P.C.F. test and 75 to the S.T.S.

The F.T.A. test is the latest of the serum tests for syphilis employing treponemal antigens. It is considered to be relatively simple to perform and the preliminary results "suggest that it has a high level of sensitivity and specificity". *R. R. Willcox*

886. **The USR Test as a Screening Test in a Public Health Laboratory**
D. WIDELOCK, J. PORTNOY, J. TRUELOVE, A. D. REYNOLDS, and J. VANDOW. *Public Health Reports* [*Publ. Hlth Rep.* (*Wash.*)] **76**, 447–452, May, 1961. 8 refs.

In the syphilis serological laboratory of the New York City Department of Health 100,000 samples of blood have been screened for antibody to cardiolipin antigen by both the V.D.R.L. slide technique and the unheated serum reagin (U.S.R.) slide test. The tests gave the same results with 98·2% of the sera. As the U.S.R. test is the simpler the authors recommend its use as a screening procedure in laboratories dealing with large numbers of sera.

All sera found to be positive were then tested by the Kolmer complement fixation test and over 1,000 samples were also titrated for complement fixation with Reiter protein antigen and with *Treponema pallidum* antigen (T.P.C.F. 50). The former test was similar in reactivity to the latter and is less expensive. *Janice Taverne*

887. **Erythromycin in Treatment of Early Syphilis**
C. H. MONTGOMERY, J. M. KNOX, G. W. SCIPLE, and E. M. VANDER STOEP. *Archives of Internal Medicine* [*Arch. intern. Med.*] **107**, 732–735, May, 1961. 7 refs.

It has been known since 1953 that erythromycin has treponemicidal properties, but there have been few clinical studies of this antibiotic. Erythromycin is a satisfactory antisyphilitic agent in large doses and this article from Baylor University College of Medicine, Houston, Texas, records an attempt to find the minimum dosage required to yield a satisfactory cure rate. A total of 148 dark-field positive cases of syphilis were studied, erythromycin stearate and propionate being used in 6 schemes of dosage. The period of observation was too short for some of the higher dosage schedules to permit a definite conclusion to be reached, but very encouraging results were obtained with a dosage of 2 g. of erythromycin stearate daily for 10 days, only 5% of patients requiring re-treatment within 6 months. Three-day (9-g.) and 5-day (10-g.) schedules were definitely inadequate; 1 g. of erythromycin propionate given daily for 10 days gave better, but not very satisfactory, results.

[This drug may provide a useful method of treatment of early syphilis in patients who cannot tolerate penicillin.] *Robert Lees*

GONORRHOEA

888. **Problems in the Use of Streptomycin in the Treatment of Gonorrhoea.** (Problèmes posés par l'emploi de la streptomycine dans le traitement de la gonococcie)
P. DUREL, V. ROIRON, and L. DELOUCHE. *Bulletin of the World Health Organization* [*Bull. Wld Hlth Org.*] **24**, 343–348, 1961. 4 refs.

Streptomycin has largely been used as the drug of first choice for the treatment of gonorrhoea in France since 1951, mainly from the fear that penicillin might mask a concomitant infection with syphilis. However, the diminishing effectiveness of streptomycin led to the present studies, which were carried out at the Institut Alfred Fournier, Paris. Sensitivity tests were performed by inoculating 25×10^6 gonococci on to horse plasma agar plates in which various graded concentrations of the antibiotics studied were incorporated. Results were read after 48 hours' incubation, complete inhibition of growth being taken as the end-point.

Streptomycin. Of 341 strains of gonococci tested, 68·9% were inhibited by a concentration of 10 μg. per ml. or less and 7·6% by 50 μg. per ml., while 22·9% grew in a concentration of 1,000 μg. per ml.

Penicillin. Of 327 strains tested, 72·5% were inhibited by 0·05 unit per ml. or less, but 26·6% required 0·1 to 1·0 unit per ml. for complete inhibition and 3 strains (0·9%) were found resistant to 1·0 unit or more per ml. [The actual concentration inhibiting these three strains is not stated.] Of the strains which had proved completely resistant to streptomycin, 76 were retested against penicillin, when 44 of them were found to be sensitive to the latter. Although no true cross-resistance between the two antibiotics was found, strains selected on a basis of streptomycin resistance tended to have lower sensitivity to penicillin than unselected strains.

Tetracycline. The 62 strains tested with this antibiotic were all found to be sensitive, as were 61 strains tested with spiramycin. Only 10 out of 154 strains of gonococci showed resistance to sulphathiazole.

In 1957 the usual treatment of gonorrhoea in France consisted in two injections of 1 g. of dihydrostreptomycin given 4 to 6 hours apart; with this dosage the failure rate was 9·8% in a series of 3,119 cases treated. In the first 10 months of 1958 (2,471 cases) the failure rate was 13·6%. Because of the rising failure rate the same dosage of streptomycin was then combined with a course of 20 g. of sulphathiazole given over 5 days. The failure rate thereupon fell to 8·2%, but rose progressively to 12·9% by September, 1960. Sensitivity tests on gonococci isolated from 242 patients treated with streptomycin alone showed that there was almost complete correlation between the carriage of streptomycin-resistant strains and clinical failure to respond to this treatment. Patients who failed to respond to streptomycin were re-treated with 600,000 units of aqueous penicillin together with 4 ml. of a broth vaccine ("propidon"). The proportion of such patients who failed to respond to this treatment was 9·2% in 1958, 11·6% in 1959, and 15·6% in the first 9 months of 1960. The authors envisage that in the future treatment of gonorrhoea streptomycin may have to be abandoned or at least reinforced with other antigonococcal agents, a situation which will entail some serious practical problems.

A. E. Wilkinson

889. **Possible Effects of Antibiotic Treatment on the Sensitivity and Growth Requirements of *Neisseria gonorrhoeae***

A. REYN and M. W. BENTZON. *Bulletin of the World Health Organization* [*Bull. Wld Hlth Org.*] **24**, 333–342, 1961. 2 figs., 20 refs.

This paper from the State Serum Institute, Copenhagen, represents an extension of work on the sensitivity of *Neisseria gonorrhoeae* previously reported by the authors (*Brit. J. vener. Dis.*, 1958, **34**, 227; *Abstr. Wld Med.*, 1959, **26**, 80). The medium used for the sensitivity tests was a chocolate agar base with 30% ascitic fluid in which antibiotics were either incorporated in graded amounts (the dilution method) or were applied as tablets containing 15 μg. of crystalline benzylpenicillin, 3 mg. of streptomycin, or 1 mg. of tetracycline (the disk method). In the former, strains were classed as sensitive if they showed 50% inhibition of growth to 0·035 μg. of penicillin per ml., 3·7 μg. of streptomycin per ml., or 0·6 μg. of tetracycline per ml. In the disk test strains were designated sensitive if they showed inhibition zones 35 mm. or more in diameter with penicillin or 36 mm. or more with the other two antibiotics.

Penicillin sensitivity tests were performed on 210 strains of gonococci isolated in 1957 and 250 in 1958. [These strains were partly selected in that they came from patients in whom treatment had been unsatisfactory.] In each year 39% of the strains showed a reduced sensitivity to penicillin and it was noted that the proportion of the most sensitive strains had fallen from 22·4% in 1957 to 12·8% in 1958. Tests for streptomycin sensitivity were requested in respect of 45 strains isolated in 1957 and 26 (65·4%) of these showed diminished sensitivity. In 1958 tests against streptomycin were performed on the 250 strains which had been tested with penicillin and 58·2% showed a lessened sensitivity to the former antibiotic; only two strains were found to be completely resistant to streptomycin and these both came from the same patient. It was noted that strains which were less sensitive to penicillin also tended to be less sensitive to streptomycin.

In June, 1957, there was a sudden increase in the number of strains isolated which showed only scanty growth on chocolate agar and fermented glucose poorly or not at all. By January, 1958, such atypical strains accounted for about 40% of all isolations received from all parts of Denmark. Serological tests on 50 of these strains showed that they were true gonococci despite their abnormal properties. Lyophilized strains which had been isolated in 1944 grew well on the medium then in use and showed normal fermentation characteristics, so that the alterations noted in 1957–8 were thought to be due to strain peculiarities rather than to deficiencies in the culture media. The atypical strains tended to be more sensitive to both penicillin and streptomycin than were typical strains selected from routine diagnostic cultures made in 1957, although sensitivity studies were difficult to perform because of the paucity of growth. The broth used in the basal medium had been made from ox or veal meat; the use of broth made from ox heart muscle resulted in considerably larger colonies and more distinct fermentation reactions, while a broth made from human placenta proved even more satisfactory. It is suggested that the appearance of these atypical strains of gonococci may have been due to penicillin therapy.

The stability of the sensitivity of gonococci to antibiotics was examined by subculturing 20 strains showing reduced sensitivity to penicillin on penicillin-free medium daily for 30 to 90 days and then comparing their sensitivity with the same strains which had been lyophilized. The subcultured strains tended to show larger inhibition zones in disk tests with streptomycin and tetracycline, but this may possibly have been due to changed growth requirements rather than to increased sensitivity. Tests against penicillin by the dilution method showed no significant differences between the subcultured and lyophilized strains. A stock strain which was relatively insensitive to penicillin kept its original level of sensitivity despite frequent subculture for over 2 years.

A. E. Wilkinson

Tropical Medicine

890. **Report on Incidence, Aetiology, Treatment and Prophylaxis of the Anaemias in the Seychelles: a Study in Iron-deficiency Anaemias and Ancylostomiasis in the Tropics**

H. Foy and A. Kondi. *Annals of Tropical Medicine and Parasitology* [*Ann. trop. Med. Parasit.*] **55**, 25–45, April, 1961. 2 figs., 9 refs.

In this interesting paper from the Wellcome Trust Research Laboratories, Nairobi, Kenya, the authors give the results of a survey of the incidence of anaemia and ancylostomiasis which they carried out in the Seychelles Islands. On the basis of 2,376 estimations the over-all mean haemoglobin level in Mahé, Praslin, and La Digue was found to be 13·2 g. per 100 ml., with a range of 3 to 19 g. per 100 ml. The proportion of people with a haemoglobin level of 8 g. per 100 ml. or less was 2·2%, which is considerably less than in Portuguese East Africa, India, or Ceylon. The lowest mean haemoglobin level was in La Digue (12·5 g. per 100 ml.), where 4·5% of the population had levels of 8 g. per 100 ml. or less. Higher average levels were found in the higher-income group, in which sanitary conditions and habits are better and, more important, shoes are more commonly worn.

The anaemia was of iron-deficiency type, and megaloblastic anaemia was not found. The major factor in the production of the anaemia was loss of blood from hookworm infestation, and dietary factors did not appear to be important. The incidence of hookworm infestation was 26% in Mahé, 41% in West Mahé, 30% in Praslin, and 40% in La Digue. These figures compare favourably with those obtained in other tropical areas and are attributed to periodic vermifuge campaigns. The anaemia responded normally to ferrous sulphate by mouth, provided the hookworm infestation and complicating conditions were also dealt with. Out-patients, however, responded inadequately, presumably because of failure to maintain treatment.

Prophylaxis of the anaemia and hookworm infestation is discussed, and fortification of the dietary rice by iron and periodic mass worming campaigns are advocated.

J. L. Markson

891. **The Treatment of Typhoid Fever**

H. A. K. Rowland. *Journal of Tropical Medicine and Hygiene* [*J. trop. Med. Hyg.*] **64**, 101–110, May, 1961.

The author utilized the large amount of clinical material available to him at the National Iranian Oil Company Hospital, Abadan, to assess the value of chloramphenicol and corticosteroids in the treatment of typhoid fever. A total of 525 patients of all ages with bacteriologically or serologically proven typhoid fever or clinical signs of the disease, such as rose spots, were admitted to a trial of 12 different treatment schedules in which chloramphenicol was given in a dosage varying from 3·9 to 15·7 mg. per kg. body weight 4- or 6-hourly for 5 or 10 days with and without prednisolone.

The incidence of complications and relapse and the death rate were found to vary with the severity of the illness before treatment. Age and sex of the patients and duration of the illness had no significant effect on the outcome, except that age may have had some influence on mortality, since 12 of the 18 deaths occurred in children aged 10 years and under. The severity of the illness on admission was itself influenced by two factors—a higher economic status and a history of previous T.A.B. inoculation being directly related to a lower percentage of seriously ill patients. Prednisolone brought about a sudden fall in temperature in 60% of the treatments in which it was given and also reduced the duration of pyrexia compared with chloramphenicol alone, but it had no other significant effect on the course of the disease. The mortality in patients seriously ill on admission was 8·4% and in those not seriously ill it was 1·3%. A relapse occurred in 53 out of 501 (10·6%) of the patients.

From this experience the author recommends that patients who are not seriously ill should receive chloramphenicol in a dosage of 7·9 mg. per kg. body weight 4-hourly for 5 days (for a patient weighing 10 stone (63·5 kg.) the dosage should be 500 mg. 4-hourly or 3 g. daily for 5 days). With this regimen cure can be expected in 95% of cases, with relapse in about 5% and complications in 5%. In patients who are seriously ill the recommended dosage is 7·9 mg. per kg. 6-hourly for 10 days (for an adult 2 g. daily for 10 days). With this dosage the expected cure rate is 97%.

H. Stanley Banks

892. **A Controlled Trial of Daraclor**

G. R. Thompson and S. B. Carter. *West African Medical Journal* [*W. Afr. med. J.*] **10**, 93–97, April, 1961. 10 refs.

In 1959 the malaria parasite rate among soldiers of the Ghana Army was 12%, but the situation in the families of the soldiers was more serious and many children under 6 years of age died from malaria due to *Plasmodium falciparum*. At the Military Hospital, Accra, the authors carried out a controlled trial of " daraclor " (a combination of chloroquine and pyrimethamine) during 2 months of the early part of the wet season in 1960 in non-commissioned officers and other ranks of 6 units of the Army. Each unit was divided into 3 equal groups and tablets were given fortnightly under medical supervision, the first group receiving 2 inert dummy tablets, the second group 2 daraclor tablets (equivalent to 300 mg. of chloroquine and 30 mg. of pyrimethamine), and the third group one daraclor tablet (150 mg. chloroquine and 15 mg. pyrimethamine) and one dummy tablet. The double-blind technique was used and neither the doctors nor the patients knew which tablets contained daraclor and which were dummies. In all subsequent cases of fever with temperature higher than 99° F. (37·2° C.), blood films were stained and examined by one of the

authors who had no knowledge of the drug that had been taken. Efforts were made throughout the trial to control all possible sources of error.

The incidence of malaria during the 8 weeks of the trial was 6·3% in the group given dummy tablets, *nil* in the 318 men given 2 daraclor tablets, and 0·3% in the 340 men given one daraclor and one dummy tablet. The last figure represented a single soldier who had parasites in his blood once only—namely, on the day after the first dose of the drug. No parasites were found for 3 weeks after the end of the trial in blood films from men with fever in either of the groups given daraclor.

It is concluded that at present one daraclor tablet every 2 weeks is fully effective as a malaria suppressant in the Ghana Army. The authors draw attention to the possibility of the development of pyrimethamine resistance with such a regimen and propose to repeat the trial after a further 9 months of fortnightly treatment in the same community.

[This is an admirably succinct account of a well controlled trial.] *L. G. Goodwin*

893. **Observations on Drug Resistant Kala-azar**
P. C. Sen Gupta and A. Chatterji. *Journal of the Indian Medical Association* [*J. Indian med. Ass.*] **36**, 225–230, March 16, 1961. 1 fig., 26 refs.

The clinical history of 5 cases of kala-azar admitted to the Hospital for Tropical Diseases, Calcutta, in which drug treatment was unsuccessful is described. In 4 of the cases cure was obtained with splenectomy followed by further courses of chemotherapy with "neostibosan" (ethylstibamine) stilbamidine, or hydroxystilbamidine. The fifth patient died following the operation. In the light of their observations the authors conclude that cases of kala-azar which do not respond to the usual treatment may be cured by splenectomy followed by prolonged courses of stilbamidine or hydroxystilbamidine. It is considered that resistance to drugs is due to a combination of parasite drug resistance, inability of the host to utilize the antimonial compounds, and lowered body resistance to the infection. *R. A. Neal*

894. **Galactose Intolerance in Kwashiorkor**
M. K. Badr El-din and M. H. Aboul Wafa. *Journal of Tropical Medicine and Hygiene* [*J. trop. Med. Hyg.*] **64**, 110–112, May, 1961. 1 fig., 8 refs.

It has been observed that the administration of milk in cases of kwashiorkor is frequently followed by diarrhoea, though the same patients tolerate animal protein when given in the form of eggs, minced meat, or liver. Previous workers have suggested that this may be due to galactose intolerance. In a study at the Faculty of Medicine, Alexandria University, Egypt, galactose tolerance tests were performed in 10 cases of kwashiorkor in infants aged 7 months to 2 years and the findings compared with those in 10 normal children of the same age group. After fasting overnight each subject received by mouth 1·75 g. of galactose per kg. body weight dissolved in water. Venous blood samples were taken immediately before and at one, 2, and 3 hours afterwards. At one hour the mean blood galactose concentration was 38·8 mg., at 2 hours 56·3 mg., and at 3 hours 25·2 mg. per 100 ml. in the patients with kwashiorkor as against 24·7, 15·7, and 0·7 mg. per 100 ml. respectively in the controls. The curve thus obtained runs above that in normal children, but well below that found in congenital galactosaemia. Examination of fasting blood revealed the presence of galactose in some cases of kwashiorkor, but none in the controls.

The authors note that in the treatment of their own cases and of many reported in the literature milk was badly tolerated. They also point to some resemblance between the symptoms of congenital galactosaemia and those of kwashiorkor. In 4 of their cases treated with animal protein, but without milk, for one week the blood galactose curve was normal. This, together with the finding that the galactose curve in kwashiorkor is still well below that in congenital galactosaemia, suggests that the loss of function is only partial and temporary. As soon as the patient recovers the liver resumes its normal function of converting galactose into glucose. A galactose-free diet containing adequate protein is recommended at the start of treatment of kwashiorkor. *William Hughes*

895. **The Rate of Recovery of Malnourished Infants in Relation to the Protein and Calorie Levels of the Diet**
J. C. Waterlow. *Journal of Tropical Pediatrics* [*J. trop. Pediat.*] **7**, 16–22, June, 1961. 23 refs.

The author has studied the influence of protein and calorie intake on the rate of recovery of malnourished infants in the West Indies. It is noted that in hospital, where the emphasis is on protein intake, the weight of these children may remain stationary over long periods. A total of 44 unselected infants under treatment in the Medical Research Council's Tropical Medicine Research Unit, Jamaica, form the subject of the present paper. The patients had all been in hospital for a month and had recovered from the acute stage of malnutrition. By this time oedema and diarrhoea had cleared up and serum albumin and cholesterinase levels had returned to normal. The children were given milk mixtures of varying protein and fat content. Sugar was added in a concentration of 10 to 30 g. per litre and olive oil or groundnut oil up to 60 g. per litre. The children's weights were recorded daily. Statistical evaluation of the results showed that gain in weight was governed by protein and calorie intake, and of these the calorie intake was the more important after the first month in hospital. In 13 of the cases nitrogen balance was studied at 30 or more days after admission. It was found that an average of 40% nitrogen was retained. Gain in weight was 40 g. per g. of nitrogen retained, which would give a "balanced" tissue gain containing 2·5% nitrogen. In theory a protein intake of 2·5 g. per kg. should be sufficient to build the body weight up to normal in the recovery stage. This is based on an average nitrogen retention of 40%, but not all children can retain such a high percentage. The author therefore advocates a daily intake of 150 Calories per kg. with a protein intake of 3 to 4 g. per kg. Vegetable oil can be used to supplement the fat content of artificial milk mixtures to bring the calorie content to the desired level. *William Hughes*

Nutrition and Metabolism

896. **Fat Infusions: Toxic Effects and Alterations in Fasting Serum Lipids following Prolonged Use**
C. S. ALEXANDER and L. ZIEVE. *Archives of Internal Medicine* [*Arch. intern. Med.*] **107**, 514–528, April, 1961. 10 figs., 27 refs.

At the Veterans Administration Hospital, Minneapolis, 5 patients with pancreatitis or malnutrition due to conditions such as ileitis and carcinomatosis received infusions of "lipomul", an emulsion of cotton-seed oil [strength not stated], intravenously in quantities of 500 to 1,200 ml. daily, 2½ to 3 hours being taken for the infusion of 500 to 600 ml. The total quantities given ranged from 9 to 35·4 litres over periods of 3 to 9 weeks. Five and 10 days respectively after the last infusion 2 of the patients, both with pancreatitis, developed a sudden illness with rigors, high fever, sore throat, tenderness about the neck, petechial haemorrhages, and epistaxis. The illnesses lasted 2 and 5 weeks respectively. A liver biopsy was performed in each case after the fat infusion and showed the presence of yellow-brown pigment, iron, and fat within the Kupffer cells. The rise in the fasting serum lipid level was essentially similar in all patients. The authors regard the intravenous administration of fat emulsions for more than 2 weeks as dangerous in view of the risk of overloading. *H. E. Magee*

897. **Senile Type Body-water Changes in Degenerative Diseases of the Central Nervous System in Middle-aged Subjects**
W. WOODFORD-WILLIAMS and D. WEBSTER. *British Medical Journal* [*Brit. med. J.*] **1**, 1126–1127, April 22, 1961. 13 refs.

In previous studies of the changes which occur in body water content in old age the authors had noted that certain degenerative diseases of the central nervous system in middle-aged subjects—particularly Alzheimer's disease, Pick's disease, and post-encephalitic Parkinsonism—produced similar physical changes as well as mental changes characteristic of senility. In the present investigation, carried out at the General Hospital, Sunderland, the findings in 7 patients with such degenerative diseases ranging in age from 40 to 59 years were compared with those in 22 healthy subjects of the same age group and those in 10 healthy subjects aged 80 to 89. The extracellular water (E.C.W.) was measured by means of sodium thiosulphate and the total body water (T.B.W.) by giving 0·4 g. of urea per kg. body weight and estimating the volume of its distribution in the tissues.

In the patients the mean value for T.B.W. was 32·1 litres, in the normal controls it was 42·7 litres, and in the elderly subjects 32·3 litres. A significant difference was found in the lean body mass as between the patients and the normal similarly aged controls, but no difference in that between the patients and the elderly. The ratio of E.C.W.:T.B.W. in the patients was 0·38 compared with 0·28 in the controls and 0·39 in the aged, although there was no significant difference between the mean E.C.W. values in the three groups. The study revealed, therefore, a true cellular dehydration in the patients with chronic degenerative diseases of the central nervous system which was comparable to that found in healthy elderly subjects. The authors consider that their findings support the view that the process of ageing is closely associated with the diminution in intracellular fluid. The inability of the cells to bind water brings about a state of condensation of the colloids ("hysteresis") and this accounts for some of the cytological changes in old age. Since colloidal condensation may also occur in degenerative neurological diseases, the authors suggest that their findings offer some confirmation of the view that senescence is primarily due to exhaustion of the diencephalon, which controls food intake, metabolism, and endocrine activity. *William Hughes*

898. **The Successful Management of Hepatolenticular Degeneration with Penicillamine: Studies on Three Generations of a Family**
J. B. STRONG JR., H. DEMPSEY, and S. R. HILL JR. *Annals of Internal Medicine* [*Ann. intern. Med.*] **54**, 198–204, Feb., 1961. 1 fig., 22 refs.

The authors describe a family at least 2 members of which had clinically overt hepatolenticular degeneration and report the results of copper metabolic studies in three generations of this family. They also describe the extensive investigations carried out on one severely ill member of the family and the success obtained with penicillamine administered over a prolonged period. The patient, a male, was 28 years old when the clinical symptoms developed rather acutely and he was admitted to University Hospital, Birmingham, Alabama. The symptoms were primarily neurological in character, but there was also laboratory evidence of severe functional impairment of the liver. The clinical condition improved dramatically with administration of penicillamine, which was continued over a 3-year period. A dosage of 0·6 g. by mouth 4 times daily on alternate days appeared to be optimal for increasing copper excretion. *H. Harris*

899. **Urinary 17-Ketosteroid and 17-Ketogenic Steroid Excretion in Obese Patients**
B. SIMKIN. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 974–977, May 11, 1961. 11 refs.

In view of the appearance during the past few years of a number of reports of increased urinary 17-ketogenic steroid excretion in obese men, women, and children and also of the frequently occurring problem of evaluating the significance of increased urinary steroid excretion in obese patients in whom the diagnosis of Cushing's syndrome is considered, the author has determined, at the Cedars of Lebanon Hospital, Los Angeles,

the 24-hour urinary 17-ketosteroid and 17-ketogenic steroid excretion in 62 consecutive unselected, untreated, obese patients and 30 healthy control patients of normal weight; the sex distribution and mean age in the two groups were comparable.

The amounts of these steroids excreted were significantly greater in the obese patients than in the control group. Thus 31% of the obese patients showed a urinary 17-ketogenic steroid excretion greater than the accepted upper limit of normal by the method used and 16% had similarly high urinary 17-ketosteroid excretion values. It is suggested that a possible mechanism to explain these findings is a positive relation between urinary 17-ketogenic steroid excretion and body weight and that the accepted ranges of normal for urinary steroid values may have to be further extended to provide for obese subjects.

There was also evidence of a clinical counterpart to the increased urinary steroid output of the obese patient, namely, in the form of signs of a mild to moderate degree of hyperadrenocorticism, as shown by menstrual abnormalities, hirsutism, hypertension, trunk obesity, acne, diabetes, and red abdominal striae. *A. G. Mullins*

900. **Cutaneous Side Effects from Use of Triparanol (MER-29): Preliminary Data on Ichthyosis and Loss of Hair**

R. W. P. Achor, R. K. Winkelmann, and H. O. Perry. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **36**, 217–228, April 26, 1961. 5 figs., 15 refs.

Triparanol inhibits the endogenous synthesis of cholesterol in the liver by preventing the conversion of 24-dehydrocholesterol (desmosterol) into cholesterol. It is therefore widely used—mainly in the United States—in hypercholesterolaemic and atherosclerotic patients, although the "ultimate clinical usefulness of this [and other similar] drugs has not yet been determined". Apart from mild nausea, headache, transient cutaneous rashes, and occasional dry skin no serious side-effects from triparanol have been observed. The present authors describe 7 cases in which there was loss of hair during treatment with this drug.

A 36-year-old man had been under observation at the Mayo Clinic for idiopathic hypercholesterolaemia and hyperlipaemia since January, 1958; he was otherwise healthy. The serum lipid levels were easily reduced, first by a diet low in animal fats and later by administration of nicotinic acid. In April, 1960, he was given triparanol in a dosage of 250 mg. daily initially, increased to 500 mg. daily. Apart from slight anorexia no side-effect was observed, but the plasma lipid levels were only slightly reduced. The dosage of triparanol was therefore increased in the 6th month of treatment to 1,000 mg. daily. Within a few weeks the patient's skin became dry and scaly and the hair, which was dark brown, became blond. During the second month on 1,000 mg. daily the skin changes progressed, with pigmentation, scalp and body hair fell out profusely, and the ability to sweat became grossly reduced. The clinical diagnosis of ichthyosis was confirmed on biopsy examination of the skin. In spite of withdrawal of triparanol the patient lost about 50% of his hair in the subsequent 2 months, but in the following month an improvement was noted in ability to sweat and softening of the skin, and the hair ceased to fall out and became darker.

Another male patient, with coronary heart disease, was given 250 mg. of triparanol daily for 3½ months. After treatment ceased an extensive dermatitis developed, with folliculitis, loss and discoloration of the hair, conjunctivitis, blepharitis, and generalized dry skin with scaliness refractory to every treatment. For the skin condition he was referred to the Mayo Clinic, but improvement in the cutaneous changes occurred only 6 months after cessation of triparanol administration. In 5 further patients (all females) treated with 500 mg. or more of triparanol excessive loss of hair was observed. None of these patients had dryness of the skin or ichthyosis. Altogether 19 patients were treated with triparanol at the Mayo Clinic for 3 to 12 months, including 6 of the foregoing. It is noted that the cutaneous reactions developed only when the daily dose was increased to 500 mg. or more. The results of liver function tests revealed no impairment.

[Similar, though milder, skin changes were recently reported after administration of nicotinic acid. These, like the changes after triparanol, became reversible when the drug was withdrawn. The cause of the cutaneous lesions may be related to the blocking of cholesterol synthesis in the liver and in the skin, thus preventing the synthesis of some essential substance required for the production of the normal epithelium.]

Z. A. Leitner

901. **Treatment of Hypercholesteremia by Nicotinic Acid. Progress Report with Review of Studies Regarding Mechanism of Action**

W. B. Parsons Jr. *Archives of Internal Medicine* [*Arch. intern. Med.*] **107**, 639–652, May, 1961. 5 figs., 36 refs.

At the Jackson Clinic, Madison, Wisconsin, the effect of more than a year's treatment with 3 to 6 g. of nicotinic acid daily was studied in 50 patients with hypercholesterolaemia in whom the serum cholesterol level was higher than 270 mg. per 100 ml. The serum total and β-lipoprotein cholesterol concentrations fell to normal levels in 80% of cases and were significantly reduced in a further 18%. The levels rose when nicotinic acid was replaced by nicotinamide, but fell once more when nicotinic acid treatment was resumed. In two patients with xanthoma tuberosum these lesions disappeared with nicotinic acid treatment, the serum cholesterol value falling from a very high to a normal level at the same time.

Cutaneous flushing occurred, but disappeared on continued treatment in most patients. Gastro-intestinal irritation was controlled by using buffered preparations of nicotinic acid. Many patients developed dryness of the skin. Enzyme tests of liver function became abnormal, but there was no histological evidence of liver damage. Glucose tolerance was diminished in some patients, but in those with adult-onset diabetes the disease was not made more severe. The serum uric acid level rose in many patients. Fibrinolysin activation did not occur with oral administration. *M. Lubran*

Gastroenterology

STOMACH AND DUODENUM

902. **Gastroesophageal Regurgitation**
S. G. TUTTLE, A. BETTARELLO, and M. I. GROSSMAN. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **176**, 498–500, May 13, 1961. 2 figs., 12 refs.

Twelve patients with complaints of heartburn were studied during symptomatic episodes by simultaneous measurement of respiration and intraluminal pressures and *p*H. A sensing device consisting of a small *p*H electrode and water-filled polyvinyl tubes was passed through the nares of each subject and placed so that the *p*H and pressure were recorded 5 cm. above the effective diaphragmatic hiatus. The patient was given a signal marker which he depressed when he experienced heartburn. Analysis of the records obtained showed that: (1) heartburn was associated with fall in *p*H below 4; (2) symptoms disappeared when the *p*H rose above this level; and (3) there were no changes in intraluminal pressures that could be correlated with *p*H. It appears that heartburn may occur with gastroesophageal regurgitation and that it need not be associated with intraluminal pressure changes.—[Authors' summary.]

903. **Effect of a Sulfated Polysaccharide on Peptic Digestion: a Study *in vitro* of Carrageenin (Ebimar)**
D. W. PIPER and B. FENTON. *Gastroenterology* [*Gastroenterology*] **40**, 638–643, May, 1961. 2 figs., 13 refs.

A study *in vitro* of the effect of a sulphated polysaccharide, carrageenin, on peptic activity is reported in this paper from the University and the Royal North Shore Hospital, Sydney. Radioactive serum albumin was used as substrate and digestion was produced by National Formulary reference pepsin. To 2 ml. of radioactive serum albumin at *p*H 2 were added 4 ml. of buffer (either Sorensen's buffer or a KCl buffer) at *p*H 2 and 1 ml. of a solution of pepsin containing 400 mg. per 100 ml. Digestion was allowed to proceed at 37° C. for 15 minutes. The influence of the sulphated polysaccharide on substrate alone and on varying concentrations of substrate and pepsin at different *p*H levels was studied, as was its effect on the electrophoretic mobility of pepsin and albumin. The authors also compared the effects of carrageenin on peptic activity with those of heparin.

Heparin, weight for weight, was more active than carrageenin in inhibiting peptic activity. Variation in *p*H between 2 and 5 had little influence on the pepsin-inhibiting properties of carrageenin. Studies of the action of carrageenin on the substrate showed that part of its effect on peptic digestion was due to the fact that it rendered the substrate unavailable for peptic digestion. The concentration of pepsin did not influence the effect of carrageenin on peptic digestion, suggesting that the sulphated polysaccharide had no action on pepsin. Varying the period of mixing the polysaccharide and pepsin had little effect on the activity of carrageenin. The electrophoretic studies showed that at *p*H 2 and *p*H 4 carrageenin had a more marked action on albumin than on pepsin.

It is pointed out that the activity of an enzyme is usually measured by the amount of products of digestion; "if these are removed by an agent, it could be due to unavailable substrate or to inactive enzyme". From the present study the authors conclude that the effect of carrageenin is due to its action on substrate. If this is so, its action would be reduced by the large amount of substrate contained in a meal and consequently it would be of relatively little value in controlling the gastric secretory response to a meal. *T. J. Thomson*

904. **Motor Function of the Gall-bladder in Patients with Cancer of the Stomach.** (Двигательная функция желчного пузыря у больных раком желудка)
E. Z. POLJAK. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **39**, 115–117, April, 1961. 6 refs.

The motor function of the gall-bladder was investigated in 35 patients, 19 male and 16 female aged 27 to 70 years, with cancer of the stomach. The tumour was situated in the cardia in 5 cases, in the body of the stomach in 7, in the antrum in 10, near the pylorus in 6, and in both the body and antrum in 7. Pyloric stenosis was present in 6 patients. In all cases the diagnosis was confirmed at operation.

The motor function of the stomach, particularly its emptying mechanism, was affected in some cases and not in others. Cholecystography was performed and the motor function of the gall-bladder was studied for 2 hours after the ingestion of raw egg-yolk. Generally speaking the gall-bladder contracts better and expels more bile (up to 85%) in patients with cancer of the stomach than in healthy subjects (30 to 60%). The most energetic contractions were observed in patients with malignant ulcer. The duration of contraction in health and in gastric cancer is 60 minutes, whereas in patients with peptic ulcer it is shortened to 30 to 45 minutes and the amount of bile expelled reaches 70 to 99%. In stenosing carcinoma of the stomach the contractions of the gall-bladder are weaker and its motor function is generally depressed because of the delayed evacuation of the stomach; similar features are observed in other types of stenosis of the pylorus. It is pointed out that disturbances of the motor function of the gall-bladder may mask the primary malignant gastric disease, particularly in icteric forms of cancer of the stomach. It is therefore recommended that studies of gall-bladder motility should always be combined with other investigations of the gastro-intestinal tract, since they can help in the differentiation of peptic ulcer from cancer.
S. W. Waydenfeld

LIVER AND GALL-BLADDER

905. **Studies in Portal Hypertension: Factors Affecting Operation Mortality**
A. G. RIDDELL and W. K. JONES. *British Medical Journal* [*Brit. med. J.*] **1**, 928–930, April 1, 1961. 5 refs.

Experience of the surgical treatment of portal hypertension in a consecutive series of 33 patients is described in this paper from the University of Manchester. In all except one of the patients hypertension was secondary to hepatic cirrhosis. Splenorenal anastomosis was carried out on 10 patients and direct portacaval shunt on the remainder. There were no deaths. These excellent results are attributed to careful preoperative preparation, control of haemorrhage during operation with immediate and quantitative replacement of blood lost, anaesthetic care (halothane and muscle relaxants were given and mechanical ventilation was used in most operations), restoration of normal blood pressure before the end of the operation, and scrupulous postoperative care. The authors describe their methods in detail.

P. C. Reynell

906. **The Portal Venous Content of Adrenaline and Noradrenaline in Portal Hypertension**
C. SHALDON, J. H. PEACOCK, R. M. WALKER, D. B. PALMER, and F. E. BADRICK. *Lancet* [*Lancet*] **1**, 957–961, May 6, 1961. 6 figs., 14 refs.

The portal venous blood levels of adrenaline and noradrenaline in portal hypertension due to cirrhosis of the liver were estimated in 18 patients undergoing portacaval anastomosis at Bristol Royal Infirmary, the blood being withdrawn while the patients were under general anaesthesia. Similar values were determined in 9 controls subjected to upper abdominal operations. The anaesthesia was similar in both groups. Adrenaline and noradrenaline were separated chromatographically and measured by bioassay techniques. Of the 18 patients with portal hypertension, 13 had adrenaline and noradrenaline levels well above the highest values found in the controls.

The authors have found that infusion of adrenaline into the human portal venous system raises the portal venous pressure without significantly affecting the arterial pressure, and it is suggested that sympathetic amines produced in the splanchnic vascular bed may play some part in maintaining the high portal venous pressures found in some of these patients. *P. C. Reynell*

907. **Neuropsychiatric Complications of Portacaval Anastomosis**
A. E. READ, J. LAIDLAW, and S. SHERLOCK. *Lancet* [*Lancet*] **1**, 961–963, May 6, 1961. 1 fig., 14 refs.

During the years 1954 to 1958 portacaval anastomosis was carried out on 21 patients at Hammersmith Hospital, London, and in this paper a follow-up investigation of the patients 6 to 60 months after operation is reported. Of the 21 patients, 19 had cirrhosis of the liver; in the remaining 2 the portal vein was obstructed at the hilum of the liver. In 20 cases haemorrhage from oesophageal varices was the indication for operation. The criteria on which the patients were selected for surgery were strict and are clearly defined.

At follow-up it was found that there had been no further haemorrhages, but in 10 patients ankle oedema had developed and 7 were jaundiced; 3 patients had died. The most serious effects were neuropsychiatric; 8 patients had had one or more episodes of coma and 6 showed evidence of portal-systemic encephalopathy at the time of examination. In only 6 patients was the electroencephalogram judged to be entirely normal. Neuropsychiatric complications were most often seen in patients over 40 and in those with the greatest postoperative deterioration in hepatocellular function.

P. C. Reynell

908. **The Relation between Age and Diffuse Liver Diseases.** (Zur Frage der Beziehungen zwischen Lebensalter und diffusen Hepatopathien)
A. BREITBACH and K. JAHNKE. *Zeitschrift für Alternsforschung* [*Z. Alternsforsch.*] **15**, 81–96, May, 1961. 12 figs., 33 refs.

Since physiological changes during life are known to occur in the structure and chemistry of the liver, the authors sought to discover whether pathological conditions and morbid biochemical changes in the liver were related to age, for which purpose they studied 521 patients admitted with diffuse hepatopathy between 1955 and 1958 to the Second Medical Clinic of the Medical Academy, Düsseldorf. Puncture biopsy confirmed the diagnosis in 481 cases. Acute hepatitis was present in 128, chronic hepatitis in 150, and cirrhosis without ascites in 204 and with ascites in 39. There was statistical evidence that acute hepatitis was most common in the young, that it ran a course of short duration, rarely became chronic, and usually ended in complete recovery. In patients in middle life (up to the 5th decade) chronic hepatitis was the commonest hepatopathy. Its average duration was 4½ months before admission to hospital, and the condition tended to be chronic from the outset. In the older age groups hepatic cirrhosis became increasingly more frequent, with an average duration of 28½ months before admission to hospital. In later decades it was often complicated by ascites. When it first appeared in old age it developed rapidly, was severe in its manifestations, and frequently progressed to hepatic failure.

A comparative study of the serum bilirubin levels and of the plasma proteins in health and in liver disease revealed that in healthy persons these levels fell as age increased. In patients with acute hepatitis they were high, while in those with chronic hepatitis they fell in later decades. In cirrhotic patients high levels were found, reaching a maximum in the 7th decade. In the healthy the erythrocyte sedimentation rate (E.S.R.) rose gradually with increasing age; in hepatitis and cirrhosis this value was markedly higher than in health. After the age of 40 the E.S.R. was higher in cirrhosis than in hepatitis. Only a slight fall in the Takáta–Ara reaction was noted in healthy old people, whereas in hepatitis the values by this test fluctuated around 60 to 70 mg. per 100 ml. at all ages and in cirrhosis there was a

steady fall from 70 to 45 mg. per 100 ml. with increasing age. Total plasma protein values decreased slightly with age in healthy persons and in patients with hepatitis, but in cirrhosis they fell steeply in patients over the age of 45. Whereas serum albumin levels decreased, albeit inconsiderably, in healthy old people, all serum globulin values increased. No marked differences were noted between α-globulin values in health and disease, but in hepatitis β-globulin values were, up to the 5th decade, higher than in health, whereas in cirrhosis they were lower, but began to rise steeply from the 4th decade onwards. In the higher decades γ-globulin values showed a moderate rise in chronic hepatitis and a marked rise in cirrhosis.

In discussing these findings the authors point out that the relationship between biochemical changes in the liver and hepatic disease is difficult to assess. In a young patient hyperbilirubinaemia may indicate gross hepatic damage if the time required for its restoration to normal is unduly prolonged. In elderly cirrhotics it can reasonably be interpreted as indicating severe reduction of function of the liver parenchyma. In the presence of dysproteinaemia it must be borne in mind that, while serum albumin is synthesized in the liver, most of the globulin, especially γ globulin, is synthesized extrahepatically; thus only when a true hypoalbuminaemia is present can reduction in parenchymal function be inferred. This condition was not met with in acute or chronic hepatitis at any age. In cirrhosis, however, there was clear evidence of a relative decrease in serum albumin and serum total protein levels in the higher age groups. The steep rise in γ-globulin values in elderly cirrhotics must not be accepted as evidence of gross hepatic dysfunction, but rather of the presence of grave constitutional disease. Diffuse hepatopathies endanger life increasingly as old age is approached. The authors urge that agents known to be potentially hepatotoxic should not be used in the treatment of the aged and that every effort be made to maintain hepatic health in such subjects by the administration of diets rich in proteins and vitamins.

E. S. Wyder

909. **Pyogenic Abscess of the Liver**

K. CRONIN. *Gut* [*Gut*] **2**, 53–59, March, 1961. 1 fig., 26 refs.

An analysis is presented of 27 cases of pyogenic abscess of the liver treated at the Radcliffe Infirmary, Oxford, during the period 1946–60, when antibiotics were generally available. Of the 27 patients (18 male and 9 female), 17 had multiple abscesses and 10 had a solitary abscess. The primary causes of the abscesses were diverticulitis (2 patients), perforated peptic ulcer (2), perforation of a simple ulcer of the colon (2), leaking intestinal anastomosis (1), necrotic growth in the rectum (2), acute appendicitis (5), acute cholecystitis (2), total gastrectomy (1), multiple pancreatic abscesses (1), and abscess of the femoral hernial sac (1). No cause was found in 8 patients.

The outstanding symptoms and signs were pain (in two-thirds of the patients), vomiting (one-third), jaundice (one-third), rigors, liver enlargement, lung signs, and subphrenic abscess. The author states that radiological examination may help in the diagnosis of liver abscess by showing: (1) elevation and fixation of the right half of the diaphragm with changes in the overlying lung; (2) distortion of the right venous pyelogram due to abscess in the right lobe; or (3) in a barium-meal examination a deformed lesser curve of the stomach due to an abscess in the left lobe.

The leucocyte count in the present series tended as a rule to be raised. There were, however, many inconsistences between the condition of the liver and the degree of leucocytosis, comparatively low counts being sometimes associated with extensive suppuration. Discussing treatment the author advises early administration of antibiotics, the introduction of which has "improved although not entirely transformed the outlook" in abscess of the liver. He states that several patients in the series survived without drainage, that selective drainage is an adjuvant, and that drainage is not always necessary. [The indications for drainage are not clearly stated.] Of the 17 patients with multiple abscesses, only 6 survived, and of the 10 with a solitary abscess, one survived, the mortality for the whole series being 75%.

[The importance of this paper lies in the author's emphasis that earlier diagnosis of the condition and a more energetic approach to the problem should reduce the mortality, although this was high over the years.]

Andrew M. Desmond

910. **Vitamin K-S (II) in Liver Disease: Effect of a New Drug on Coagulation Defects**

J. C. HOAK and J. R. CARTER. *Archives of Internal Medicine* [*Arch. intern. Med.*] **107**, 715–722, May, 1961. 2 figs., 28 refs.

An investigation of the value of a new drug, S-(2-methyl - 1:4 - naphthoquinonyl - 3) - β - mercaptopropionic acid (vitamin K–S (II)), in the management of the clotting defect in parenchymal liver disease is described in this paper from the State University of Iowa College of Medicine, Iowa City. The study was carried out on 33 patients (27 men and 6 women) aged 33 to 83 (mean 50) years, of whom 27 had Laënnec's cirrhosis, 2 post-hepatic necrosis, one biliary cirrhosis, one chronic hepatitis, and one cirrhosis of unknown type. All had severe liver disease with deficiency of the clotting accelerator activity of the plasma. The drug was given intravenously in doses of 10 mg. twice daily or by mouth in doses of 100 mg. twice daily. When transfusions were given the drug was administered only after the effect of the donor blood on the serum accelerator levels had disappeared. Clotting accelerator activity was measured periodically during treatment. The test system, which was believed to measure Factors V and VII, was prepared from defibrinated oxalated human plasma to which was added 2 g. of potassium oxalate per 100 ml. This preparation was aged 12 to 14 days at room temperature or 5 to 6 days at 37° C. It had no Factor-V or Factor-VII activity, but still contained prothrombin. Plasma prothrombin concentration and various other factors were also estimated.

Treatment with vitamin K–S (II) was effective in correcting Factor-V and Factor-VII deficiencies in 21 (63%) of the patients and a fair response was obtained in 6 others (18%). There was little effect on the plasma pro-

thrombin level and no toxic side-effects were noted. Failure of vitamin K–S (II) to improve plasma clotting accelerator activity was regarded as an indication of very severe liver disease and a poor prognosis. Of the 6 patients in this category, 5 died within 45 days of admission. *A. S. Douglas*

911. **Tolbutamide in Cirrhosis of the Liver**
I. SINGH, K. B. SEHRA, and S. P. BHARGAVA. *Lancet* [*Lancet*] **1**, 1144–1146, May 27, 1961. 5 refs.

An increased deposition of glycogen in liver cells which may have a beneficial effect on liver-cell metabolism has been observed following tolbutamide administration. The authors of this paper from the Armed Forces Medical College, Poona, and Irwin Hospital, New Delhi, have studied the effect of this drug in animals and in patients with liver disease. In dogs pre-treatment with tolbutamide gave statistically significant protection against liver-cell damage induced by administration of carbon tetrachloride. However, the drug was of little value in limiting the extent of liver-cell damage once it had occurred. Tolbutamide in a dosage of 1 to 1·5 g. daily was given to 55 patients with "nutritional" cirrhosis and fluid retention. Each patient acted as his own control by receiving treatment with this drug alternating with a placebo. Improvement in appetite and a lessened tendency to accumulate fluid were noted in 50 of the 55 patients while receiving tolbutamide, 42 of them becoming free from ascites and oedema. This improvement was associated with a rise in the serum albumin level and a variable fall in the serum globulin level. When tolbutamide was replaced by the placebo there was a return to the pre-treatment condition.

The authors consider that tolbutamide exerts a beneficial effect on hepatic function, perhaps by facilitating the utilization of amino-acids. *K. R. Gough*

912. **A Study of Prognosis in Alcoholic Cirrhosis.** (Étude sur le pronostic de la cirrhose alcoolique)
Y. BOQUIEN, P. PERRIN, J. HOREAU, J. GUILLON, D. HERVOUET, —. MENARD, —. DELHUMEAU, and —. LEBODIC. *Revue internationale d'hépatologie* [*Rev. int. Hépat.*] **11**, 183–205, 1961. 11 refs.

Alcoholic cirrhosis due to excessive wine drinking is a serious problem in France. For the present study the authors were able to collect 521 cases of this disorder admitted to the Centre Hospitalier Régional, Nantes, in the 3 years 1954 to 1956 inclusive, of which 288 occurred in men and 233 in women; the majority of the patients (355) were aged between 40 and 60, while 44 were under 40 and 122 over 60 years. At the time of follow-up in 1959 351 of the 521 patients were dead, 75 were alive, and 95 could not be traced. Only 33 of the survivors were leading a relatively normal life, the remainder being permanently or intermittently ill owing to their cirrhosis, while one was so alcoholic that he could not be interviewed. In the authors' view the best chance of survival is total abstinence from alcohol. Of 342 patients, 219 (64%) died within 6 months of admission to hospital, 27 died between 6 months and one year, 96 between one and 2 years, and only 17 survived for more than 4 years.

Of the factors influencing prognosis the most significant were the initial response to treatment, especially in regard to diuresis, the presence or absence of haemorrhage from the gastro-intestinal tract, the ratio of esterified to non-esterified cholesterol levels in the blood, and the results of serum flocculation tests. A blood prothrombin level below 50% [method of estimation not stated] was a bad prognostic sign. The over-all impression is one of the gravity of this condition. *G. S. Crockett*

913. **The Use of Radioactive Tagged Lipids in the Differential Diagnosis of Jaundice**
D. BERKOWITZ, D. M. SKLAROFF, and H. J. TUMEN. *Gastroenterology* [*Gastroenterology*] **40**, 513–517, April, 1961. 1 fig., 28 refs.

The differential diagnosis in 50 patients with various types of jaundice was studied at Hahnemann Medical College Hospital, Philadelphia, by means of the radioactive triolein tolerance test. In 25 cases the cause of the jaundice was an extrahepatic block, confirmed at operation or necropsy, while in the other 25 the clinical course and the result of biopsy examination indicated that the jaundice was due to hepatitis (viral or drug-induced), cirrhosis, or malignancy. The test used consisted essentially in the administration of a meal containing about 25 μc. of ^{131}I-labelled triolein in an emulsion of peanut oil or in a capsule containing 0·5 ml. of the radioactive fat; the resulting radioactivity was determined in venous blood.

In the patients with jaundice amenable to surgery fat absorption was impaired, the triolein absorption curve being invariably flat and the level of radioactivity in the stools high. Thus in 18 cases of carcinoma of the pancreas the mean maximum radioactivity in the blood was only 2·3%, while in 6 cases of stone in the common duct the mean value was 3·7%. In non-surgical jaundice higher mean values for maximum blood radioactivity were recorded, this value in 17 cases of viral hepatitis being 9·6% and in 6 cases of drug hepatitis 12·5%. One single case of carcinoma of the bile duct showed low values, whereas one of biliary cirrhosis and one of metastatic carcinoma of the liver showed high maximum blood radioactivity appropriate to their group. There was no correlation between the total serum bilirubin level and the amount of fat absorbed. From these results it is concluded that in most instances the test distinguished clearly between cases of surgical and those of non-surgical jaundice and in conjunction with other tests would seem to be of very definite diagnostic help. Special comment is made, however, on the case of one severely ill patient with jaundice due to chlorpromazine who gave values typical of the surgical group.
W. H. Horner Andrews

914. **The Acute Cholestatic Syndrome**
R. A. JOSKE, L. R. FINLAY-JONES, and E. G. SAINT. *Medical Journal of Australia* [*Med. J. Aust.*] **1**, 609–618, April 29, 1961. 9 figs., bibliography.

From the Royal Perth Hospital (University of Western Australia) the authors describe 15 cases of a syndrome in which the results of clinical and biochemical investiga-

tion suggested an extrahepatic type of obstructive jaundice, but in which no mechanical biliary obstruction could be demonstrated at operation or necropsy. This syndrome has been previously described in the literature under various names, such as pseudo-obstructive jaundice, cholangiolitic hepatitis, and intrahepatic obstructive jaundice.

The cases described occurred in 9 males and 6 females ranging in age from 23 to 64. Although the clinical picture resembled that of infective hepatitis, fever was unusual, there was no disturbance of the serum proteins, flocculation tests gave negative results, and the serum alkaline-phosphatase level was not raised above 40 units except in 2 of the cases in which there were complicating factors. The liver was enlarged in 13 cases. The jaundice did not last longer than 2 months. At laparotomy, performed in 10 of the 15 cases, the bile ducts and gall-bladder were found to be collapsed. Biopsy examination revealed some increase in fibroblasts in the portal tracts, and bile thrombi in the biliary canaliculi were common.

The literature is extensively reviewed and the pathogenesis discussed. The suggested aetiological factors included a sensitivity reaction to drugs such as chlorpromazine, some alteration in the physical characteristics of the bile by methyltestosterone and norethandrolone (" nilevar "), and invasion by a virus with a predilection for the bile ductules rather than for the liver cells.

Steroid treatment may help, and 12 of the 15 patients recovered fully. The one death occurred in a man aged 61, and it is noted that the condition was generally much more severe in males than in females, in whom it usually ran a benign course. *G. S. Crockett*

INTESTINES

915. **Pneumatosis Intestinalis: a New Concept**
W. S. KEYTING, R. R. MCCARVER, J. L. KOVARIK, and A. L. DAYWITT. *Radiology* [*Radiology*] **76**, 733–741, May, 1961. 13 figs., 4 refs.

The literature on pneumatosis intestinalis is reviewed and 7 cases are briefly recorded, 4 of which were seen within one month at the Veterans Administration Hospital, Denver, Colorado. The condition is considered to be due to an escape of air into the subserous layer of the intestine, into cystic accumulations which displace the bowel, or along the mesentery. The " air " has a high nitrogen content, the oxygen originally present having been absorbed. Of the cases described, there was air dissection along the superior mesenteric artery in 4, the inferior mesenteric in one, and along all the major abdominal vessels in one. In one case the pneumatosis was due to mucosal ulceration with leakage of air subserously occurring in a sigmoid volvulus.

The authors consider that the condition in the majority of cases arises directly from gastro-intestinal obstruction and perforation, but that in the remaining cases it is almost always due to air reaching the gut from the lungs. Since in many cases there is associated chronic pulmonary disease, they carried out experiments to show that in such cases rupture of pulmonary alveoli may lead to the passage of air into the mediastinum and thence retroperitoneally along the arterial routes to the wall of the bowel. They therefore conclude that three mechanical factors are responsible for all cases of pneumatosis: (1) obstruction with perforation, (2) trauma, resulting from sigmoidoscopy or biopsy, or (3) development as secondary to pulmonary disease with air dissection downwards along a vascular route to the bowel. *Thomas Hunt*

916. **Phenylbutazone Suppositories in Treatment of Non-specific Proctitis**
J. HANKISS. *British Medical Journal* [*Brit. med. J.*] **1**, 1280–1282, May 6, 1961. 21 refs.

The author of this paper from the University School of Medicine, Debrecen, Hungary, has already had success with phenylbutazone by rectal infusion in the treatment of ulcerative colitis. He now describes the results obtained with this drug in the form of suppositories in non-specific proctitis.

A total of 22 patients, who were selected on the basis of the results of sigmoidoscopy, examination of the faeces, and barium-enema and helminthological examination, were divided into 3 groups: (1) 11 patients with non-specific proctitis; (2) 7 patients with non-specific proctc-sigmoiditis or proctitis associated with ulcerative colitis, the disease being limited to the most distal part of the colon; and (3) 4 patients in whom proctitis was secondary to a minor local cause. Suppositories containing 200 mg. of phenylbutazone were given twice daily, later reduced to once daily; if the patient became symptom-free the dose was reduced to one suppository every 2 days and later to 2 suppositories in a week. If there was no improvement within 7 to 10 days treatment was discontinued for a few days and then resumed with a " combined-formula " suppository, which initially contained 200 mg. of phenylbutazone and 8 mg. of prednisolone; in the more recent cases 100 mg. of argento-protein (" protargol ") was also added to the combined suppository.

The response to treatment was judged by the findings on clinical examination and sigmoidoscopy. Of the 11 patients with proctitis in the first group, 7 showed rapid remission, which remained complete in 4 cases and could be maintained in 3 by the use of one to 2 suppositories a week; in 2 cases improvement was maintained by the combined suppositories only. The patients in the second group with ulcerative colitis did not respond satisfactorily, and only 2 patients with procto-sigmoiditis remained symptom-free after treatment. In the third group the initial measure was to give appropriate treatment to the underlying cause; thereafter, phenylbutazone suppositories, preferably in the combined form, gave good results in 3 out of the 4 patients.

The author concludes that this form of treatment has proved to be very effective in chronic proctitis; the combined type of suppository brought about improvement in some patients who failed to derive any benefit from suppositories containing phenylbutazone alone.
Joseph Parness

Cardiovascular System

917. **Clinical Features of Pulmonary Embolism**
D. W. BARRITT and S. C. JORDAN. *Lancet* [*Lancet*] **1**, 729–733, April 8, 1961. 2 figs., 15 refs.

The symptoms of pulmonary embolism with infarction may include hypotension, faintness, substernal discomfort, breathlessness, pleural pain, and haemoptysis. Pleural pain and haemoptysis are only accompanied by hypotension when a massive embolism has taken place. A rise in jugular venous pressure and a large fall in systemic blood-pressure are the commonest signs of massive embolism, and tachycardia nearly always accompanies the appearance of the first symptom. Auscultation of the heart is of little value in diagnosis. The electrocardiogram (ECG) may show characteristic changes—a combination of S_1, Q_3, T_3, and right ventricular T-wave inversion, with or without right bundle-branch block, in lead V_1. These changes are not seen unless there is clinical evidence of right-heart stress. In only about half the cases of pulmonary embolism is the ECG of diagnostic value. The bedside radiograph is helpful in confirming a lung lesion.

In a series of 72 patients, 2 with suppurative pneumonia were mistakenly thought to have an embolism. Clinical evidence of thrombosis in leg veins was common; but in 16 patients, no abnormal signs were found. Fourteen per cent of the patients had superficial thrombophlebitis and 24% had long-standing changes in the skin of the legs as a result of varicose veins.—[Authors' summary.]

918. **Specific Antibodies in Heart-disease**
E. N. EHRENFELD, I. GERY, and A. M. DAVIES. *Lancet* [*Lancet*] **1**, 1138–1141, May 27, 1961. 2 figs., 19 refs.

The authors have investigated, at the Hadassah Medical School, Jerusalem, the incidence of haemagglutinating antibodies against human heart antigen by the tanned-cell technique in the serum of 150 patients with heart disease, 32 with other diseases, 62 older patients with non-cardiac chronic diseases, and 30 normal control subjects.

Inhibition studies showed that the antibodies were organ-specific but were not species-specific. None of the non-cardiac patients or the normal controls gave a definite positive haemagglutination reaction ($\geq$1:10), and only 15 showed a doubtful positive or non-specific reaction ($\leq$1:5). On the other hand a positive reaction was obtained in 24 cardiac patients: 5 out of 15 patients with rheumatic heart disease, 2 out of 20 who had undergone cardiac surgery, 12 out of 53 with acute myocardial infarction, 3 out of 33 with chronic coronary arterial disease, and 2 out of 3 with pulmonary heart disease; 9 of these patients had titres of over 1:20, and titres of up to 1:1,280 occurred. None of the 20 patients with inactive rheumatic heart disease gave a positive reaction. In 4 cases the raised antibody level persisted for months or years after coronary infarction, in 2 the rise was transient, and in one case of rheumatic fever the antibody level rose following the acute clinical episode.

Animal experiments showed that although 4 out of 20 rabbits developed haemagglutinating antibody on injection of homologous heart tissue in Freund's adjuvant no myocardial damage was seen. The authors suggest that cardiac damage renders heart tissue antigenic and conclude that the results of serological and follow-up studies support the concept that these circulating antibodies are a result and not a cause of heart disease.

G. L. Asherson

919. **The ABC Cardiogram of Right Ventricular Hypertrophy**
L. H. HARRIS. *British Heart Journal* [*Brit. Heart J.*] **23**, 285–290, May, 1961. 3 figs., 10 refs.

At Broadgreen Hospital, Liverpool, an analysis of the ABC electrocardiogram (Trethewie, *Brit. med. J.*, 1958, **2**, 1428; *Abstr. Wld Med.*, 1959, **25**, 333) in 83 cases of mitral stenosis (69 with a mean pulmonary arterial pressure greater than 20 mm. Hg and 14 with normal pressure) and in 7 cases of pulmonary stenosis with high right ventricular pressure revealed that the ABC Lead showed evidence of right ventricular hypertrophy in 90% of cases compared with only 64% in a 12-lead display plus Lead V3R. An R:S ratio of 1:2 or greater in Lead A, B, or C is considered to be diagnostic of right ventricular hypertrophy. Maximal right ventricular activity seemed to be shown in Lead A, while T-wave inversion in Lead A or C indicated the more severe grades of hypertrophy. Although experience with the ABC leads is as yet too limited to justify their substitution for what is described as " the standard display ", it is considered that these leads (or at least Lead A) should be added to the routine cardiogram.

William A. R. Thomson

920. **Relationship between Arterial Pressure and Negative U Waves in Electrocardiograms**
A. J. GEORGOPOULOS, W. L. PROUDFIT, and I. H. PAGE. *Circulation* [*Circulation*] **23**, 675–680, May, 1961. 3 figs., 10 refs.

This study reported from the Cleveland Clinic Foundation, Ohio, demonstrates that there is a direct relationship between arterial blood pressure and the degree of negativity of U waves in the electrocardiogram (ECG) of hypertensive patients, regardless of the severity and type of hypertension. The correlation was observed during the treatment of 45 hypertensive patients in whose ECGs negative U waves became upright with successful therapy. Temporary conversion of negative U waves to positive was obtained during the hypotensive phase produced by an intravenous infusion of sodium nitroprusside or of guanethidine. In one hypertensive patient with atrial extrasystoles it was noted that negative U waves became upright with each premature beat, during

which the arterial pressure fell, whereas the beat following the extrasystole, which was associated with a higher arterial pressure, showed even more sharply inverted U waves than before. *T. Semple*

921. **Relative Ischaemia in the Hypertrophied Heart**
J. D. Woods. *Lancet* [*Lancet*] **1**, 696–698, April 1, 1961. 2 figs., 11 refs.

The hypertrophied heart is extremely dependent on an adequate blood supply, which must increase as the heart grows larger. Normally an increase in the coronary blood flow is achieved by an elevation of the aortic blood pressure or by a lowering of coronary peripheral resistance. The physiological limits of these two mechanisms determine the maximum amount of blood transported by a coronary vessel of given size. In this paper from Fremantle Hospital, Western Australia, a study is reported of the relationship between the size of the right coronary artery and the weight of ventricular muscle it supplies. The right coronary artery was found by injection studies to supply up to 46% of the left ventricle by weight as well as the whole of the right ventricle and was thus affected by hypertrophy of either or both chambers. This artery could be measured more accurately than the left because of the absence of early major branching. With the aid of an injection technique the area of muscle supplied by this artery was dissected out and weighed, while the greatest apparent diameter of the lumen of its first inch (2·5 cm.) was measured, the material consisting of 2 normal hearts and 19 hearts exhibiting severe ventricular hypertrophy without significant atheroma of the right coronary artery. It was found that only in the healthy hearts was the cross-sectional area of the artery directly related to the weight of muscle supplied. In hypertrophy there was no corresponding increase in the bore of the vessel.

The findings support the view of Fishberg that one of the primary factors in hypertrophic heart failure is progressive ischaemia due to relative narrowness of the supplying artery. This factor is present irrespective of the primary cause of the hypertrophy. *T. Semple*

922. **Subacute Bacterial Endocarditis: Clinical and Laboratory Observations in 27 Consecutive Cases Treated with Penicillin V by Mouth**
E. L. Quinn and J. M. Colville. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 835–842, April 27, 1961. 2 figs., 16 refs.

The results obtained with phenoxymethylpenicillin in the treatment of endocarditis due to *Streptococcus viridans* are reported in this paper from the Henry Ford Hospital, Detroit. The drug was given by mouth to 27 patients in a dosage of 1·2 g. 4-hourly; the majority of the patients also received streptomycin intramuscularly in a dosage of 1 to 2 g. daily. This dosage of penicillin was well tolerated and produced serum concentrations comparable to those obtained with 100,000 units of aqueous procaine benzylpenicillin intramuscularly every 6 hours. Definite bacteriological cure was achieved in 21 and probable cure in 3 of the 27 patients. Of the remaining 3 patients, one failed to absorb amounts of penicillin adequate to produce a minimum serum inhibitory activity of 16 times the concentration necessary to inhibit the infecting organism, while 2 died from complicating conditions—congestive cardiac failure and active rheumatic pancarditis respectively—before treatment was completed.

The authors emphasize the need for determining the serum concentration or the serum inhibitory activity in each patient receiving penicillin by mouth in order to ascertain adequate intestinal absorption. *I. Ansell*

923. **Value of Mercaptomerin and Intravenous Aminophylline in Cardiac Oedema Resistant to Other Diuretics**
J. G. Domenet, D. W. Evans, and O. Brenner. *British Medical Journal* [*Brit. med. J.*] **1**, 1130–1133, April 22, 1961. 9 figs., 15 refs.

At the Queen Elizabeth Hospital, Birmingham, 35 patients with congestive cardiac failure were treated thrice weekly with an intramuscular injection of 2 ml. of mercaptomerin followed by an intravenous injection of aminophylline 2 hours later. The aminophylline was given in a dose of 0·5 g. in 20 ml. of carbon dioxide-free water and was injected slowly, at least 10 minutes being taken for the injection. All the patients had previously been treated with other diuretics, which had failed to produce a continuous diuresis. They were treated with bed rest and digitalis and were given a restricted salt diet and potassium supplement. In 28 cases the patient responded to the combined treatment with sustained diuresis and clinical improvement and all but one patient lost weight during the treatment. In 31 cases out of 34 in which weight was recorded daily the maximum rate of loss occurred with this regimen. The authors recommend it in any case of heart failure in which mercurial diuretics, alone or in combination with benzthiazide derivatives, have failed to clear the oedema. The treatment should be withheld if the blood urea level exceeds 70 mg. per 100 ml. *G. S. Crockett*

VALVULAR DISEASE

924. **Pure or Predominant Mitral Incompetence in Chronic Endocarditis.** (L'insuffisance mitrale pure ou très prédominante par endocardite chronique)
R. Froment, A. Perrin, J. Pasquier, J. Normand, and P. Michaud. *Malattie cardiovascolari* [*Mal. cardiovasc.*] **2**, 13–47, Jan. [received May], 1961. 25 figs., 23 refs.

In this paper, based on 162 cases, seen at the Hôpital Edouard Herriot, Lyons, the authors discuss rheumatic mitral incompetence in chronic endocarditis. Five major types are recognized from anatomical and functional studies, as follows.

(1) Valvular sclerosis, (*a*) with extensive fusion of commissures, contraction of chordae, and often calcification; (*b*) without fusion of commissures but with diffuse contraction of the cusps, especially the aortic, or segmental sclerosis.

(2) Annular type, which is due to distension of the mitral ring, with relatively little abnormality of the cusps or commissural fusion. (3) Dislocation of a cusp,

usually the mural cusp, with elongation or rupture of the chordae. (4) A type with aneurysmal dilatation of the left atrium. (5) The type with obliterating atrial thrombosis.

The diagnostic criteria are a murmur heard at the apex and in the axilla, seldom at the base, which is pansystolic, beginning before the aortic valve opens and continuing after the second sound, and is often accompanied by a thrill and sometimes by a short apical diastolic murmur. In some cases the murmur occupies only the later part of systole. Radiography demonstrates the degree of dilatation of left atrium and left ventricle and the amount of calcification. In the absence of aortic disease, electrocardiographic evidence of left ventricular predominance indicates mitral incompetence, but this predominance is not always present. Cardiac catheterization of the right heart does not give reliable information, although a wedge pressure curve may show the typical findings with a large v wave, as may also left atrial puncture. Left heart catheterization may confirm the absence of a systolic gradient. Dye dilution curves may give confirmation of regurgitation, but these again may not be accurate, especially if rhythm is irregular. In some cases there is hypertrophy of the right ventricle with pulmonary hypertension. Selective angiography performed by left ventricular puncture allows of estimation of the degree of reflux by comparing the opacification of the left atrium with that of the aorta.

In regard to outlook, many patients live to old age, or die of intercurrent disease. Others die during an attack of acute rheumatism. Those who succumb to heart failure usually do so after a considerable latent period (average 18 years). Operation is indicated in cases showing pure mitral regurgitation with progressive haemodynamic insufficiency. Operative technique must be based on exact pathological anatomy. Extracorporeal circulation and deep and light hypothermia have all been used. Perhaps the most convenient technique is one which allows careful examination while the heart is beating, correction while arrested, and confirmation when the heart is beating again. The various procedures employed include annuloplasty, valvuloplasty, and plication. *M. Meredith Brown*

925. **Pulmonary Ossific Nodules in Mitral Valve Disease**
R. W. GALLOWAY, E. J. EPSTEIN, and N. COULSHED. *British Heart Journal* [*Brit. Heart J.*] **23**, 297–307, May, 1961. 7 figs., 29 refs.

A retrospective survey was made of the chest radiographs of 204 patients admitted to the Regional Cardiac Centre, Liverpool, for assessment of mitral valve disease. In 27 of these patients definite ossific nodules were present in the lung fields, this finding, taking the sex ratio in the series as a whole, being three times as common among males as among females. Evidence of pulmonary venous hypertension, such as a history of paroxysmal nocturnal dyspnoea, septal lines visible on the radiographs, or a mean pulmonary wedge pressure exceeding 20 mm. Hg, was found in the majority of the 27 cases. Apart from the raised incidence in men and the indications of increased pulmonary venous pressure, calcification was not related to other common manifestations of cardiac disease.

Histological examination showed a deposition of osteoid tissue developing in alveoli, but there was no indication of previous haemosiderosis or non-ossific deposits of calcium. In patients for whom serial radiographs were available no changes were noted over an observation period varying from one to 5 years.

J. Robertson Sinton

926. **The Value of Quinidine in the Prevention of Atrial Fibrillation after Mitral Valvuloplasty**
H. BLACK, B. LOWN, and A. F. BARTHOLOMAY. *Circulation* [*Circulation*] **23**, 519–524, April, 1961. 1 fig., 22 refs.

Working at the Peter Bent Brigham Hospital, Boston, the authors investigated the efficacy of quinidine in the management of atrial fibrillation occurring after mitral valvotomy by comparing treated and untreated groups in two series of patients, one being studied retrospectively and the other prospectively. In the retrospective study the records were examined of 255 patients in normal sinus rhythm who had undergone mitral valvotomy. Of these, 226 were placed in Grade III (severe cardiac disability not reaching irreversible congestive failure or complete invalidism) and 29 in Grade IV (the most severely affected group). The first 38 patients of this series received no quinidine, but its administration was afterwards introduced as a routine measure. Of these 38 patients (all Grade III), 50% had postoperative atrial fibrillation, while of the 188 Grade-III patients treated with quinidine (usually starting within 6 hours of treatment in doses of 0·8 to 1·2 g. a day), fibrillation was recorded in only 22%. There was no evidence for the greater effectiveness of a dosage higher than 0·8 g. a day.

In the prospective study 82 patients were paired as they presented for valvotomy and one member of each pair was allocated to the treatment and the other to the control group by the toss of a coin. In the treatment group quinidine sulphate was administered in a dosage of 0·3 g. thrice daily on the day before operation and 0·3 g. 4 times a day on subsequent days. The method of sequential analysis was used and the assumptions made that the treatment (quinidine or control) should be accepted if there were less than 20% of failures, and rejected if there were more than 40% of failures. On these criteria treatment with quinidine was accepted at the 5% level of confidence after 14 cases and at the 1% level after 36. Control treatment was rejected at the 5% level of confidence after 20 cases. A runs analysis confirmed the consistency of the trend in the quinidine-treated group.

In the combined series, among the 308 Grade-III patients, 42% of the 79 who were untreated developed postoperative fibrillation compared with 22% of the 229 who were treated with quinidine, this difference being statistically significant. Among the 39 Grade-IV patients the figures were 60% for controls and 50% for the treated group, the difference being non-significant. There was no significant difference in the mean time of onset of fibrillation between treated and untreated groups. Blood levels of quinidine were estimated in 27 patients; there

was no evidence of a low level being associated with the onset of fibrillation. Preoperative atrial fibrillation and episodes of palpitation were associated with an increased risk of postoperative fibrillation in both treated and control groups, and in both the incidence of fibrillation was higher in males than in females. There was no difference between treatment and control groups in the incidence of spontaneous reversion.

The authors conclude that there is good evidence for the efficacy of quinidine and state that of every 100 patients in sinus rhythm who are subjected to valvotomy, quinidine reduces the incidence of postoperative atrial fibrillation from 42 to 22. Eight of the 22 may be expected to revert spontaneously to sinus rhythm when the rate is controlled with increased dosage of digitalis, in 12 normal rhythm may be restored by increasing the dose of quinidine after the 10th day, and only 2 will remain permanently in fibrillation. It is suggested that a dosage of 0·8 to 1·2 g. a day seems to be adequate.

R. H. Cawley

927. **Effects of Intravenous Lanatoside-C upon Cardiodynamics in Patients with Mitral Stenosis and Regular Sinus Rhythm**

M. A. GREENE, A. GORDON, and A. J. BOLTAX. *American Heart Journal* [*Amer. Heart J.*] **61**, 622–633, May, 1961. 27 refs.

The haemodynamic effects of intravenous lanatoside-C were studied in 7 female patients with isolated mitral stenosis and in regular rhythm at the Bronx Hospital, New York. All the patients had effort dyspnoea and 2 had evidence of right ventricular failure at the time of the study, but no patient was taking digitalis. After a preliminary hospital stay of 2 weeks right-heart catheterization was carried out and the various haemodynamic parameters assessed before and after the injection of 1·2 to 1·4 mg. of lanatoside-C into the pulmonary artery over a period of 2 to 3 minutes. In order to establish the degree of chance variation in the measurements an additional 29 right-heart catheterizations were carried out on a control group of patients with varying types of heart disease and varying degrees of congestive failure, and the results in this group were used to provide the confidence limits for the 7 patients with mitral stenosis.

Control measurements before the injection of lanatoside-C showed a low cardiac output and increased peripheral resistance in all 7 patients and pulmonary hypertension in 6 of the 7 patients. After the injection the pulmonary arterial diastolic and mean pressures decreased significantly in 3 patients and the pulmonary wedge pressure and right ventricular end-diastolic pressure also fell significantly in 2 of them. In the 4 remaining patients there was no alteration in pulmonary diastolic and mean pressures, but in 2 there was a significant increase in pulmonary systolic pressure associated with an increase in stroke volume and cardiac output. Two main factors are suggested to account for these haemodynamic changes: (1) improved right ventricular function results in increased filling of the pulmonary bed, explaining the increase in pulmonary systolic pressure since the pulmonary outflow is obstructed by a stenosed mitral valve; and (2) bradycardia produced by lanatoside-C allows increased emptying of the pulmonary bed and left atrium, which results in a fall of pulmonary diastolic, mean, and wedge pressures.

The authors conclude that through the mediation of the above mechanism digitalis is of value in patients with mitral stenosis and regular rhythm who have developed right ventricular failure. *Gerald Sandler*

DISTURBANCES OF RHYTHM AND CONDUCTION

928. **Atrial Fibrillation and Pregnancy**

P. SZEKELY and L. SNAITH. *British Medical Journal* [*Brit. med. J.*] **1**, 1407–1410, May 20, 1961. 20 refs.

An analysis is presented of 60 pregnancies (in 50 patients) complicated by transient or permanent atrial fibrillation. These were observed in a series of 760 consecutive pregnancies in 550 patients with rheumatic heart disease admitted to Newcastle General Hospital between 1942 and 1959. The incidence of heart failure and embolism and the maternal and foetal mortality are discussed, particularly in relation to cardiac rhythm. Atrial fibrillation had been present before pregnancy in 31 of the 60 instances and heart failure occurred either during pregnancy or in the puerperium in 8 of them; there was onset of atrial fibrillation during pregnancy or in the puerperium in 29 instances and heart failure developed in 21. Embolism was more common in the patients with atrial fibrillation than in those in whom sinus rhythm was maintained, resulting in a higher maternal mortality (5% as against 1%) and foetal loss (20% as against 8·5%). The authors consider that with better management leading to restoration of sinus rhythm and anticoagulant prophylaxis maternal mortality in these cases can be greatly reduced. Since 1950 they have had no maternal deaths in 39 pregnancies complicated by atrial fibrillation. *A. I. Suchett-Kaye*

929. **Preliminary Report on the Use of "Alupent" in the Treatment of Disturbances of Atrio-ventricular Conduction in the Heart.** (Erste Erfahrungen über Alupent bei der Behandlung der Av-Leitungsstörungen des Herzens)

G. FRIESE and R. THORSPECKEN. *Deutsche medizinische Wochenschrift* [*Dtsch. med. Wschr.*] **86**, 1045–1050, May 26, 1961. 4 figs., 46 refs.

From the University Medical Clinic, Heidelberg, the authors report a trial of a new sympathicomimetic drug, "alupent" (1-hydroxy-1-(3:5-dihydroxyphenyl)-2-propylaminoethane). In 10 subjects with healthy hearts a dose of 20 mg. by mouth raised the pulse rate perceptibly after 10 minutes and had a maximum effect after 55 minutes. The drug is not destroyed in the gastro-intestinal tract and is very stable in solution.

Clinically, in 16 cases of disordered cardiac rhythm alupent was shown to have a dromotropic action, that is, it improves auricular–ventricular (A–V) conduction, and a chronotropic action, that is, influencing favourably all cardiac foci in which impulses are inhibited. Of 8 cases of total A–V block, normal sinus rhythm was

restored in 2, total block was converted to partial block of the Wenckebach type in one, and although total block persisted in 4, the heart rate was increased; alupent failed to benefit the remaining case in which total heart block was associated with severe atherosclerosis, and this patient died. In 4 of the 8 patients the heart block was accompanied by Stokes–Adams attacks and in 3 of them alupent brought about disappearance of these attacks and in the fourth a reduction in their frequency. Of a further 4 with partial heart block, normal rhythm was re-established by means of alupent in 3, but one remained refractory. The drug was also of benefit in 2 cases of sino-auricular block, as well as in 3 cases of bradycardia associated in one with Stokes–Adams attacks and with auricular flutter and heart failure in the other 2.

Although the series was admittedly small, partly because disorders of cardiac rhythm are not very common and partly because when present they may not require any therapy, the authors suggest, on the basis of a careful study of their patients over a relatively long period, that alupent may be of considerable value in (1) acute disturbances of rhythm, such as cardiac standstill, Stokes–Adams attacks, and heart block, when it should be administered by slow intravenous infusion (5 to 10 mg. in 250 ml.), or in emergency by intracardial injection in doses of 0·25 to 0·5 mg., reinforced with 20 mg. by mouth every 2 hours; (2) in less acute cases it may be given intramuscularly in doses of 0·5 to 1·0 mg. or orally in a dosage of 20 mg. every 2 hours; and (3) for the long-term maintenance of normal rhythm in a dosage of 10 mg. every 2 to 4 hours. *E. S. Wyder*

930. **Treatment of Heart Block and Adams–Stokes Syndrome with Sustained-action Isoproterenol**
S. Dack and S. R. Robbin. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **176**, 505–512, May 13, 1961. 3 figs., 10 refs.

At present major episodes of the Adams–Stokes syndrome are best treated by means of the continuous intravenous infusion of isoproterenol followed by intramuscular or sublingual administration of the same drug at frequent intervals for maintenance therapy. In order to obtain a more lasting effect the authors, working at Mount Sinai Hospital, New York, have used sustained-action tablets of isoproterenol given by mouth in the maintenance treatment of 15 patients with atrioventricular heart block and the Adams–Stokes syndrome. The frequency with which the drug was administered and its dose depended on the severity of the disorder and ranged from 60 mg. every 3 hours to 30 mg. 3 times a day. The average dosage was 30 mg. every 4 hours. Though tremor and tachycardia occurred in 4 cases, in only 2 of these did the drug have to be stopped. This is in contrast to sublingual therapy, which is more likely to cause troublesome side-effects. Electrocardiographic control showed that in 5 cases a significant objective beneficial effect was obtained after the ingestion of the sustained-action tablet.

The authors conclude that the administration of sustained-action tablets in these cases offers definite advantages over sublingual therapy. *J. B. Wilson*

CORONARY DISEASE AND MYOCARDIAL INFARCTION

931. **The Secretion and Excretion of Adrenaline and Adrenaline-like Substances in Patients Suffering from Coronary Disease.** (Выделение адреналина и адреналиноподобных веществ у больных с коронарной недостаточностью)
D. Ê. Kagan and G. A. Kvitko. *Терапевтический Архив* [*Ter. Arh.*] **33**, 71–74, April, 1961. 10 refs.

The investigation reported was carried out on 105 patients (87 men, 18 women) suffering from varying degrees of coronary arterial disease and ranging in age from 30 to 62 years. Shaw's method was used for the quantitive estimation of adrenaline and adrenaline-like substances in the blood and the same method as modified by Utevsky and Kagan for the estimation of the substances in the urine. The concentrations of these substances both in the blood and in the urine were within the normal limits in the majority of cases between attacks, but during attacks both values were increased in 83% of cases. *A. Orley*

932. **Preliminary Clinical Trials with a New Coronary Vasodilator, Benziodarone.** (Premiers essais cliniques avec un nouveau vasodilatateur coronarien: la benziodarone)
P. Dailheu-Geoffroy and J. Nataf. *Presse médicale* [*Presse méd.*] **69**, 971–973, May 6, 1961. 3 figs., 6 refs.

The authors present a preliminary report on the results obtained with a new coronary vasodilator, ethyl-2-(hydroxy-4 diiodo-3:5-benzoyl)-3-benzofuran (" benziodarone "), in 40 patients with cardiac pain associated with myocardial infarction in 16 cases, status anginosus in 10, angina of effort in 13, and aneurysm of a sinus of Valsalva in one. The preparation was given by mouth for periods varying between 8 weeks and 6 months, the initial dose being 200 mg. 3 times daily, with a minimum daily maintenance dose after 6 to 8 weeks of 400 mg. Judged by the general condition of the patients, their response to effort tolerance tests, the reduction in the amount of trinitrin required, and improvement in the electrocardiogram, the results were considered to be excellent in 16 cases, good in 11, moderately beneficial in 7, and *nil* in 6. Thus a satisfactory improvement was achieved in 67% of the whole series, results being least satisfactory in the group of patients with angina of effort. In 85% of cases the drug was considered to be superior to other commonly employed coronary vasodilators which were given for comparison. *A. Schott*

933. **The Types of Blood Supply to the Heart.** (К вопросу о типах кровоснабжения сердца)
A. V. Smol'jannikov and T. A. Naddačina. *Архив Патологии* [*Arh. Patol.*] **22**, 17–24, No. 10, 1960. 4 figs., 17 refs.

The authors report a radiographic study of the arterial system of the human heart for which they used a 5% solution of lead carbonate in gelatin as the contrast medium. In all, 301 hearts from patients who had died

of various forms of coronary insufficiency and 120 normal hearts were examined by this method. On the basis of their findings a new and extended classification of the types of distribution of the coronary arteries is suggested. In addition to the generally recognized left, right, and medial types, the authors distinguish two intermediate ones, which they designate " medial left " and " medial right ". They claim that the presence of these two additional types is important not only from the pathological, but also from the clinical point of view. Thus the number of anastomoses between the branches of the main coronary arteries is greater in the intermediate types than in either the left or right types, and they were able to demonstrate that the proportion of cases having " pure " left and right types only was higher (28·6% as against 15·0%) in the patients with fatal coronary insufficiency than in the normal control hearts.

A. Swan

934. **Lipid Patterns in Myocardial Infarction and Angina Pectoris**
T. R. E. Pilkington and H. Koerselman. *Lancet* [*Lancet*] **1**, 1019–1029, May 13, 1961. 9 refs.

In this study, carried out at St. George's Hospital, London, the serum total cholesterol and low-density lipoprotein levels were measured in 46 males with clinical and/or electrocardiographic evidence of myocardial infarction and compared with those in 48 males of the same age group and of similar height and weight with angina pectoris but no evidence of myocardial infarction. A random selection of the patients were treated with a diet low in saturated and high in unsaturated fats. This diet resulted in a striking lowering of the blood lipid levels. No blood lipid examinations were performed in the first group until 8 weeks after the myocardial infarction. The mean serum total cholesterol level was slightly higher (but not significantly so) in this group than in the group with angina. The mean serum level of low-density lipoproteins was nearly 15% higher in the former than in the latter group. When the low-density lipoproteins were divided into those of Sf 0 to 12 and those of Sf 12 to 400 the mean level of the latter was more than 32% higher in the group with myocardial infarction than in the group without. It is concluded that the rise of the serum lipid level in myocardial infarction is not only quantitatively higher than in uncomplicated coronary disease, but is qualitatively different.

C. Bruce Perry

935. **Myocardial Response to Cigarette Smoking in Normal Subjects and Patients with Coronary Disease**
T. J. Regan, M. J. Frank, J. F. McGinty, E. Zobl, H. K. Hellems, and R. J. Bing. *Circulation* [*Circulation*] **23**, 365–369, March, 1961. 16 refs.

At Wayne State University College of Medicine, Detroit, the myocardial response to cigarette smoking in coronary artery disease was studied in 8 patients who were habitual smokers, a group of 6 patients, also smokers, who had recovered from an acute benign illness serving as controls. In both groups catheterization of the coronary sinus and right atrium was carried out and coronary blood flow was determined by the nitrous-oxide desaturation technique followed immediately by determination of cardiac output (Fick). Two standard non-filter cigarettes were smoked in about 25 minutes, smoking being maintained during coronary blood flow sampling and while the heart rate, arterial blood pressure, and the left ventricular lead were monitored.

Similar changes in blood flow occurred during smoking in both groups of patients and there was no evidence to suggest that myocardial infarction was precipitated by vascular changes caused by cigarette smoking.

J. Robertson Sinton

936. **Atrial Infarction of the Heart**
Chi Kong Liu, G. Greenspan, and R. T. Piccirillo. *Circulation* [*Circulation*] **23**, 331–338, March, 1961. 8 figs., 21 refs.

The authors describe 6 cases of coronary thrombosis in which the changes in the electrocardiogram suggested atrial infarction as well as involvement of the ventricular wall. Suggestive changes were the appearance of an atrial arrhythmia and depression of the P wave in precordial leads. These changes were sometimes extremely transient and daily records were required for diagnosis.

The diagnosis of atrial infarction was confirmed at necropsy in all the cases. Both atria were involved in 3 cases, the right atrium in 2, and the left atrium in one.

J. Robertson Sinton

HYPERTENSION

937. **The Prognosis of Essential Hypertension Treated Conservatively**
M. Sokolow and D. Perloff. *Circulation* [*Circulation*] **23**, 697–713, May, 1961. 9 figs., 33 refs.

The prognosis in essential hypertension treated solely by conservative methods is discussed in this paper from the University of California School of Medicine, San Francisco, with reference to the findings in 439 patients (143 males and 296 females) followed up for at least 5 years or until death. The initial blood pressure was classified arbitrarily as Grade I (150 to 200 mm. Hg and 90 to 110 mm. Hg), Grade II (200 to 250 mm. Hg and 110 to 130 mm. Hg), and Grade III (over 250 mm. Hg and 130 mm. Hg), all pressures being recorded after the patient had rested in the supine position for 20 minutes. During the follow-up period other signs of hypertension were recorded, such as eye changes, abnormalities in the electrocardiogram (ECG), cardiac enlargement, history of cardiac failure, and evidence of atherosclerosis in cerebrovascular accidents or coronary thrombosis.

At the end of the 5-year follow-up period 161 patients were dead—78 (55%) of the 143 men and 83 (28%) of the 296 women. Mortality varied directly with the height of the blood pressure initially, the severity of the eye changes, and the alterations in the ECG. Evidence of heart failure was associated with a mortality of 100%, but there was no direct relationship between mortality and age at appearance of hypertension.

A casual finding was that the obese patient with hypertension appeared likely to live longer than the non-obese.

J. Robertson Sinton

938. **Severe Hypertension Treated with Ganglion-blocking Drugs in a General Hospital**

J. D. K. NORTH, J. C. P. WILLIAMS, and R. N. HOWIE. *British Medical Journal* [*Brit. med. J.*] **1**, 1426–1429, May 20, 1961. 5 figs., 17 refs.

The results of treatment with ganglion-blocking drugs in 284 patients with severe hypertension are reviewed in this paper from Auckland Hospital, Auckland, New Zealand. The review covers the period 1951–8 and in all cases treatment was given for at least 12 months. Of the 284 patients, who all attended a special hypertension clinic established on the principles recommended by Smirk (*Brit. med. J.*, 1954, **1**, 717; *Abstr. Wld Med.*, 1954, **16**, 132), 35 had malignant hypertension with Grade-IV fundal changes, 71 had pre-malignant hypertension with Grade-III changes, and 171 had severe benign hypertension with lesser degrees of retinopathy; 7 patients were not graded. The series consisted of 125 males and 159 females, of whom the great majority were aged between 40 and 60 years. In regard to drugs, hexamethonium was used originally, later pentolinium and mecamylamine or pempidine, and since 1954 rauwolfia alkaloids have been added to the regimen of treatment in most cases.

The survival rates for one, 3, and 5 years were 82, 56, and 44% respectively in the malignant group, 84, 67, and 57% respectively for the pre-malignant group, and 98, 93, and 81% respectively for the group with benign hypertension. Radiological assessment showed improvement in the heart size in 21% of the cases, no change in 65%, and a deterioration in the remaining 14%. Results based on the electrocardiographic changes were less impressive, 39% of the patients showing improvement and 15% deterioration. Nearly all the patients experienced some side-effects from the ganglion-blocking drugs, but in only 12% of cases were these effects serious enough to cause limitation of the patients' activities, and no less than 78% of surviving patients are able to lead a normal life, that is, continue in their employment or, if women, manage the house and family responsibilities.

A. I. Suchett-Kaye

939. **Treatment of Severe Hypertension with Guanethidine**

A. J. BARNETT, P. KINCAID-SMITH, F. H. LUMB, and I. G. LYALL. *Medical Journal of Australia* [*Med. J. Aust.*] **1**, 681–686, May 13, 1961. 33 refs.

This report from the Baker Medical Research Institute, Alfred Hospital, Melbourne, gives details of the authors' experience with the use of the sympathetic blocking agent guanethidine in 32 patients over periods up to 14 months. These 32 patients had severe hypertension (6 had previously had papilloedema) and all but 3 had received treatment with ganglion-blocking drugs for months or years before they were given guanethidine. The drug was given in two regimens of dosage—high (75 mg. or more daily) and low (50 mg. or less daily). The majority of patients receiving either of these regimens responded satisfactorily, so far as blood-pressure control was concerned, within 2 weeks. The maximum dose used was 175 mg. daily, and with this limitation on dosage the blood pressure could not be controlled in 3 cases. Side-effects included muscular weakness, tiredness, and diarrhoea in about half the patients, and the drug was stopped because of side-effects in 3 cases. Tolerance was not a prominent feature.

In most cases blood-pressure control was achieved with guanethidine to a degree comparable to that obtained with ganglion-blocking drugs in the same patients, and postural faintness was found to occur with similar severity and frequency. [No comment is made about possible hypotension on effort.]

In 9 cases a slight increase in the blood urea level (15 mg. per 100 ml. or more over the highest pre-treatment value) was noted which persisted after 3 months, and 2 patients were observed to develop proteinuria. The significance of this finding is not clear.

M. Harington

940. **The Effect of Guanethidine in the Treatment of Hypertension: a Study of Twenty-five Patients**

M. STEVENSON, N. GOODMAN, D. FINKELSTEIN, and S. BELLET. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **7**, 386–391, March, 1961. 3 figs., 8 refs.

A clinical study of the treatment with guanethidine of 25 out-patients suffering from persistent hypertension is reported from the Philadelphia General Hospital. Twenty patients had essential hypertension, 4 chronic pyelonephritis, and one hypertension due to toxaemia of pregnancy. Fifteen were women and 10 were men and their ages ranged from 31 to 73 (average 55) years. Previous hypotensive medication was discontinued at least a fortnight before the pre-treatment recumbent blood pressure was recorded. The diastolic levels ranged in 12 instances from 100 to 118 mm. Hg and in 13 from 120 to 160 mm. Hg (the average for the 25 cases being 120 mm. Hg).

Guanethidine was administered orally in one or two daily doses. The dosage, which varied initially from 10 to 25 mg. daily, was adjusted at weekly intervals until an amount was found that controlled the blood pressure with avoidance of severe symptoms due to the drug. This final maintenance dose varied from 5 to 175 mg. (average 80 mg.) daily; up to 50 mg. was required by 10 patients, between 50 and 100 mg. by 5 [6 according to the tabulated data], and 100 mg. or more by 10 [9 according to the tabulated data]. After 6 to 28 (average 12) weeks' treatment a reduction in blood pressure was found in all cases. In the recumbent position the average fall of the systolic level was 22 mm. Hg and of the diastolic 14 mm. Hg (that is, a mean reduction to $90{\cdot}6\pm12{\cdot}5$ and $89{\cdot}4\pm9{\cdot}2$% of the pre-treatment values), which was not statistically significant. In the erect position the average fall in pressure was 49 mm. Hg systolic and 24 mm. Hg diastolic (to $77{\cdot}6\pm9{\cdot}9$ and $80{\cdot}7\pm10{\cdot}7$% of the pre-treatment values), which was statistically significant. The hypotensive effect was thus predominantly postural. In many of the cases a higher dosage of the drug than the final maintenance dose produced even more marked reductions in standing blood pressure (to means of $71{\cdot}3\pm10{\cdot}5$% of the pre-treatment systolic value and $75\pm9{\cdot}1$% of the pre-treatment diastolic value), but resulted in unpleasant symptoms. Postural hypotensive

effects were observed as early as 72 hours after an effective dose and up to 5 days after discontinuance of the drug.

Of the 25 patients, 14 complained of dizziness on rising in the morning and on standing and one case of syncope is mentioned, but in most cases this was mild and was eliminated by lowering the dosage. The only other side-effects were nausea or vomiting in 4 cases and diarrhoea in 2. [This incidence of diarrhoea is low in comparison with that reported in other trials of guanethidine.] The pulse rate fell by an average of 16 to 20 beats per minute in all cases. Acquired tolerance necessitating cautious increments in dosage appeared to develop in some of the cases.

The authors consider the disadvantages of the drug to be the marked individual variation in the effective dosage, which could not be clearly correlated with the degree of hypertension, and an unpredictability in the hypotensive effect of a dosage increment; the risk of severe postural hypotensive effects; and the apparent development of tolerance other than in patients with mild degrees of hypertension [a contention not fully substantiated in the article].

The authors tentatively conclude that guanethidine has a place in the treatment of the more severe type of hypertension in conjunction with chlorothiazide and reserpine or their analogues in patients who have failed to respond in the first place to the latter drugs alone. Guanethidine is not recommended, however, for the mild case of hypertension or for use without other hypotensive agents. *J. J. Segall*

941. **The Hypotensive Effects of Chlorothiazide and Hydrochlorothiazide: a Critical Comparison**
J. M. Bryant, N. Schvartz, M. Roque, L. Fletcher, H. Fertig, and D. P. Lauler. *American Journal of Cardiology* [*Amer. J. Cardiol.*] 7, 392–395, March, 1961. 6 refs.

From the New York University Post-Graduate Medical School and Bellevue Hospital, New York, comes a report on a method of evaluation of the relative effectiveness of antihypertensive drugs in 78 ambulatory patients, 45 women and 33 men aged 36 to 79 (average 58) years. The known duration of hypertension was from one to 26 (average 9·9) years; none of the patients had evidence of gross renal insufficiency. Patients were observed over a period of 1 to 3 years during which they received at different times both chlorothiazide and hydrochlorothiazide, in some cases with the addition of reserpine in low dosage. The values reported are the averages of blood-pressure readings taken with the patients recumbent but unrested. Initial control periods without therapy preceded treatment periods, which were followed in patients showing a hypotensive response to a drug by a further control period with placebo administration for 1 to 3 months until the blood pressure returned to a level similar to that observed after the initial control period. Doses were administered by mouth three times a day.

The efficacy of chlorothiazide alone, 750 mg. daily, was compared with that of hydrochlorothiazide alone, 75 mg. daily, in this way in a group of 47 patients of average age 58±5 years and with an average duration of hypertension of 10·5±6·8 years. The initial control period averaged 4·5±3 months, after which the average blood pressure was 189±31/109±15 mm. Hg. This fell to 171±28/102±13 mm. Hg with chlorothiazide administered for periods of 1 to 15 (average 2·2) months and to 159±29/97±15 mm. Hg with hydrochlorothiazide given for 1 to 5 (average 1·8) months. A group of 26 patients of average age 59±13 years and average duration of hypertension 12·1±7·5 years who had failed to respond to both drugs alone were treated with chlorothiazide, 750 mg., and reserpine, 0·375 mg., daily for 1 to 12 (average 6·2) months and with hydrochlorothiazide, 75 mg., and reserpine, 0·3 mg., daily for 1 to 8 (average 2·3) months. The average blood pressure after an initial control period of 4·7±3·4 months was 192 ±31/109±19 mm. Hg; after chlorothiazide and reserpine it was 170±33/96±17 mm. Hg, and after hydrochlorothiazide and reserpine it was 161±31/92±15 mm. Hg. The average decrements in blood pressure (in mm. Hg) for the four methods of treatment in order of effectiveness were thus 31/17 with hydrochlorothiazide and reserpine, 30/12 with hydrochlorothiazide, 22/13 with chlorothiazide and reserpine, and 18/7 with chlorothiazide. The same order of effectiveness was found in a group of 19 patients who were evaluated for all four methods, the decrements being respectively 35/19, 28/11, 25/13, and 11/7 mm. Hg. The only side-effects encountered with chlorothiazide and hydrochlorothiazide were symptoms of indigestion in a few patients and a skin reaction in one. Administration of reserpine produced a weight gain in a majority of patients, increased appetite frequently, and caused nasal congestion in 9% of patients. [There is some discrepancy, which is not explained, between the total number of patients studied (78) and the totals in the three groups (47, 26, and 19).]

The authors conclude that in the dosages used chlorothiazide and hydrochlorothiazide both had a statistically significant hypotensive effect, that of hydrochlorothiazide being the greater, with fewer side-effects than are seen with reserpine; and that the addition of reserpine augmented the hypotensive effect to a degree that was statistically significant for systolic values and possibly also for diastolic values. They recommend the initiation of antihypertensive therapy with hydrochlorothiazide alone and the subsequent addition of reserpine only if a satisfactory response is not obtained.

[It should be noted that the cases were relatively mild as judged by the pre-treatment diastolic levels of pressure and duration of hypertension. The work is interesting as a method of evaluating and comparing the antihypertensive activity of drugs in ambulatory patients.]
J. J. Segall

942. **Gallop Sounds in Hypertension and Myocardial Ischaemia Modified by Respiration and Other Manoeuvres**
E. Parry and P. Mounsey. *British Heart Journal* [*Brit. Heart J.*] 23, 393–404, July, 1961. 9 figs., 23 refs.

Clinical Haematology

943. **Increase in Haemoglobin A_2 Appearing after Homograft of Foetal Haemopoietic Tissue**
J. M. Bridges, D. W. Neill, and H. Lehmann. *British Medical Journal* [*Brit. med. J.*] **1**, 1349–1352, May 13, 1961. 5 figs., 8 refs.

Damage to the bone marrow caused by chemotherapeutic agents administered for the treatment of cancer may itself be treated by the transfusion of erythropoietic cells. At St. Bartholomew's Hospital, London, 8 patients with severe marrow failure following intensive chemotherapy for various malignant conditions were given transfusions of foetal liver suspension as a source of active erythropoietic tissue. In all of the 3 survivors in whom marrow function recovered haemoglobin A_2 temporarily appeared in the blood, the amount of which gradually increased and then gradually declined. The evidence, which is discussed, strongly favoured the conclusion that this haemoglobin was derived from the foetal cells. It is suggested that no foetal haemoglobin was produced because the cells were in an environment in which there was no synthesis of foetal haemoglobin; the production of haemoglobin A by the foetal cells is at a relatively lower level and this may account for the synthesis of haemoglobin A_2. The authors conclude that the appearance of haemoglobin A_2 may prove to be a useful indicator of the survival and maturation of transfused foetal haematopoietic tissue in all patients so treated and suggest that this technique could supplant, and certainly supplement, the rather limited method now available, which can be used only in those patients in whom dissimilarity in the blood groups of donor and host is present.

R. B. Thompson

944. **Primary Myeloid Metaplasia**
A. J. Bowdler and T. A. J. Prankerd. *British Medical Journal* [*Brit. med. J.*] **1**, 1352–1358, May 13, 1961. 6 figs., 26 refs.

From University College Hospital, London, brief case histories of 12 male and 4 female patients are presented to illustrate the very varied clinical and haematological features shown by patients with the common histological manifestation of myeloid metaplasia. Precise classification of these features is difficult because of the many intermediate forms which may occur and also because of the remarkable changes which may take place in any one patient during the course of the disorder.

The authors describe their cases in five main groups: (1) bone marrow failure with hepatosplenomegaly (5 cases); (2) polycythaemic type (3 cases); (3) presentation with leucocytosis (1 case); (4) presentation with thrombocythaemia or megakaryocytosis (4 cases); and (5) presentation with haemolytic anaemia (3 cases). They state that myeloid metaplasia seems to be a "benign multifocal neoplasia" and the fact that it may precede fibrosis of the bone marrow is against the view that it develops in order to compensate for marrow fibrosis. That excessive production of any of the formed elements of the blood may occur in a patient with myeloid metaplasia also indicates that the latter is not compensatory. The authors prefer the name "primary myeloid metaplasia" to "myelofibrosis" and discuss the nature and diagnosis of the disorder. Treatment of the condition requires a nice assessment of the various factors present in any given case. Splenectomy may be helpful if there is proven excessive haemolysis in that organ, but the authors used it in only one of their cases. Treatment by splenic irradiation had to be abandoned in one patient because of nausea and malaise. Steroids and radioactive phosphorus were found to be the most useful therapeutic agents; the former may be particularly helpful in controlling haemolysis and the latter when there is polycythaemia or thrombocythaemia, but its use is undesirable if there is marrow failure. These patients are very sensitive to busulphan ("myleran") and 4 patients treated with it showed marked falls in the leucocyte and platelet counts. In the authors' opinion clinical improvement is not likely to be achieved with this drug.

R. B. Thompson

945. **Hypersplenism Due to Infection: a Study of Five Cases Manifesting Hemolytic Anemia**
J. H. Jandl, H. S. Jacob, and G. A. Daland. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 1063–1071, May 25, 1961. 7 figs., 46 refs.

From Boston City Hospital and Harvard Medical School the authors report the cases of 5 patients suffering from systemic infections—miliary tuberculosis, subacute bacterial endocarditis, infectious mononucleosis, infective hepatitis, and psittacosis respectively—in whom transient haemolytic anaemia developed, associated with splenomegaly. All finally recovered except the patient with subacute bacterial endocarditis (whose spleen, weighing 483 g., was removed surgically both for purposes of diagnosis and for relief of a possible source of infection).

All 5 patients are shown to have had the following features in common—anaemia of definitely haemolytic type, spherocytes in the circulating blood, splenomegaly, and "increased red-cell sequestration in the spleen". The last point is important. By labelling some of the erythrocytes with radioactive chromium (^{51}Cr) it was shown that their life-span was moderately diminished, especially in the early, active, febrile stages of the systemic disease. The suggestion is put forward that splenomegaly (or "hypersplenism") due to the infection was the primary event in the pathogenesis of the haemolytic process, and the authors discuss various hypotheses of causation, all of which have been advanced by others. These include (*a*) suppression of bone-marrow function; (*b*) hypertrophy and over-activity of the reticulo-endothelial cells in the enlarged spleen; and (*c*) increased

"erythrostasis" in the splenic sinusoids (Ham and Castle), leading to spheroidal change in a proportion of erythrocytes which have undergone repeated detention in the spleen without sufficient time in the general circulation to recover. These cells are in danger of being permanently trapped in the spleen and destroyed. The final suggestion is that the haemolytic anaemia in these 5 patients was due to damage to erythrocytes during their repeated passage through the enlarged spleen, and that the process may be regarded as one form of "hypersplenism" in infections characterized by prolonged stimulation of the reticulo-endothelial system.

J. W. McNee

ANAEMIA

946. **Testosterone-induced Remission in Aplastic Anemia of Both Acquired and Congenital Types: Further Observations in 24 Cases**

N. T. SHAHIDI and L. K. DIAMOND. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 953–967, May 11, 1961. 10 figs., 23 refs.

At the Children's Hospital Medical Center, Boston, 24 children with aplastic anaemia (decrease or absence of blood-forming elements in the bone marrow and peripheral pancytopenia but without splenomegaly, hepatomegaly, or lymphadenopathy) were treated with testosterone in a dosage of 1 to 2 mg. per kg. body weight daily in addition to steroids and blood transfusion as required. In 17 the condition was considered to be acquired and in 12 of them a marrow toxin was identified (chloramphenicol, dicophane (DDT), or naphthalene). In 13 cases there was a slow but sustained increase in the reticulocyte count and in 9 this was associated with a rise in the haemoglobin concentration until further transfusion was unnecessary, a slower rise in absolute neutrophil and platelet counts over a period of months, and a variable repopulation of the bone marrow with cellular elements. In these 9 patients it was possible to withdraw treatment altogether after 2 to 15 months and no further medical care has been needed (follow-up period 3 to 22 months). The remaining 8 children died from haemorrhage or infection. Virilization, flushing, and acne were seen in all cases, especially in the boys, and in 2 patients headaches and papilloedema developed which were relieved by administration of diuretics. All these side-effects subsided promptly when testosterone was withdrawn.

In 7 patients the aplastic anaemia was judged to be constitutional or congenital because of associated congenital defects and a positive family history or history of purpura dating from the neonatal period. Haematological remission was obtained in all these patients. (Treatment had been given for 5 to 20 months at the time the report was written.) In some cases a reduction in dosage was possible, but in none could treatment be stopped altogether.

[These are impressive and exciting results. The possibility of avoiding side-effects by using relatively non-virilizing anabolic hormones is under investigation.]

P. C. Reynell

947. **Oral Treatment of Pernicious Anaemia with Vitamin-B_{12}–Peptide**

N. K. SHINTON. *British Medical Journal* [*Brit. med. J.*] **1**, 1579–1582, June 3, 1961. 1 fig., 36 refs.

It has been claimed by Heathcote and Mooney (*Lancet*, 1958, **1**, 982; *Abstr. Wld Med.*, 1958, **24**, 276) that patients with pernicious anaemia can be adequately maintained by oral treatment with vitamin B_{12} (cyanocobalamin) in doses as low as 10 μg. daily if the vitamin is given in the form of a complex with peptide derived from fermentation, but this has subsequently been disputed. A trial of vitamin B_{12}–peptide has therefore been carried out in the Coventry Hospital Group on 17 consecutive cases of proven pernicious anaemia in relapse. The serum vitamin-B_{12} level was below 100 $\mu\mu$g. per ml. in all cases, in none of which were neurological complications present. The vitamin B_{12}–peptide complex was given by mouth in tablet form in doses of 100, 200, or 500 μg. per day to all the patients for 15 days, during which the serum vitamin-B_{12} level was repeatedly estimated. This showed a progressive rise and there was an increase in haemoglobin value, erythrocyte count, and packed cell volume. The responses to the complex were compared with those observed in a previous trial to the oral administration of vitamin B_{12} alone in similar doses; only with doses of 100 μg. per day was there a significantly better response to the peptide preparation.

In 10 of the cases a 3- to 18-month maintenance trial was carried out. All patients receiving daily doses of 200 and 500 μg. reached normal haematological values and the serum vitamin-B_{12} levels at the end of the trial were roughly the same as at 15 days. Only one out of 5 patients given 100 μg. daily failed to attain normal haematological values; this patient was given successful parenteral therapy. One patient given 200 μg. daily for 3 months developed peripheral neuritis in the upper limbs even though the serum vitamin-B_{12} level was 170 $\mu\mu$g. per ml.

It is concluded that vitamin B_{12} when given orally either in the crystalline form or as a peptide complex in "generous daily doses" is as satisfactory as any other oral preparation. However, "parenteral therapy remains the most reliable method of treating pernicious anaemia".

R. B. Thompson

948. **The Aetiology of Retrobulbar Neuritis in Addisonian Pernicious Anaemia**

A. G. FREEMAN and J. M. HEATON. *Lancet* [*Lancet*] **1**, 908–911, April 29, 1961. 21 refs.

Retrobulbar neuritis is a well recognized though uncommon complication of pernicious anaemia. Three factors suggest that it is not caused solely by deficiency of vitamin B_{12} (cyanocobalamin)—namely: the overwhelming male preponderance in contrast to the equal sex incidence of pernicious anaemia and subacute combined degeneration of the cord; the condition is not related to the duration, presence, or degree of anaemia or to the neurological complications: and none of the patients in reported cases has been a non-smoker. The authors consider that the additional factor in the causation of the neuritis is tobacco, and they present evidence

that tobacco amblyopia and retrobulbar neuritis occurring in pernicious anaemia are identical conditions. In support of this hypothesis, they describe 2 illustrative cases seen at the Bristol Eye Hospital. In the first patient, a pipe-smoker, tobacco amblyopia developed which did not improve when tobacco was withdrawn; 9 months later pernicious anaemia developed. Both conditions responded to cyanocobalamin. In the second patient, also a pipe-smoker, tobacco amblyopia developed during treatment for pernicious anaemia with " anahaemin " and improved when cyanocobalamin was substituted. It is therefore suggested that deficiency of cyanocobalamin renders the optic nerve sensitive to the toxic effects of tobacco. *J. L. Markson*

949. **The Aplastic Crisis in Sickle-cell Anaemia**
J. E. MacIver and E. J. Parker-Williams. *Lancet* [*Lancet*] **1**, 1086–1089, May 20, 1961. 4 figs., 26 refs.

In patients with sickle-cell anaemia the haemoglobin level and reticulocyte count are very constant over long periods, but episodes of severe anaemia are sometimes seen, particularly in children, when these patients are followed for a long time. These " anaemic crises " are accompanied by a reticulocytopenia and a reduction in the degree of jaundice. Basically there are only two types of crisis in sickle-cell anaemia: (1) the clinical or painful crisis due to erythrostasis of sickled erythrocytes, resulting in infarction of various tissues, and (2) the aplastic or haematological crisis, in which the delicately poised balance between production and destruction of erythrocytes is disturbed. In an aplastic crisis the cells containing largely sickle haemoglobin are destroyed more rapidly than those with less sickle and more foetal haemoglobin. There is evidence that the erythrocyte population in sickle-cell anaemia is not homogeneous owing to the non-uniform distribution of foetal haemoglobin in these cells. Thus the initial dramatic increase in anaemia in these patients may be due to the rapid destruction of a highly susceptible group of erythrocytes.

Of the 12 cases of aplastic crisis described in this paper from University College of the West Indies, Jamaica, 10 were seen within a period of less than 7 months, suggesting that the syndrome may be commoner than has previously been supposed. The fact that 7 of the patients belonged to 3 families is thought to suggest that infection may play an important aetiological role. Bacteriological and virus studies however failed to produce any definite evidence of recent infection, although one patient was apparently suffering from infectious mononucleosis. *A. W. H. Foxell*

950. **Red-cell Fragmentation Syndrome: a Condition of Multiple Aetiology?**
S. P. Lock and K. M. Dormandy. *Lancet* [*Lancet*] **1**, 1020–1024, May 13, 1961. 3 figs., 13 refs.

During the past few years several workers have reported the occurrence of a syndrome in young children consisting of haemolytic anaemia, thrombocytopenia, and oliguria. In all the patients bizarrely fragmented erythrocytes have been found in the peripheral blood film. At necropsy in one series of 7 fatal cases bilateral renal cortical necrosis was invariably found, but in another series of 6 cases, 2 of which were fatal, only widespread platelet thrombi were seen.

The present authors describe 5 further cases seen during a recent 18-month period at the Hospital for Sick Children, Great Ormond Street, London. The patients (3 boys and 2 girls, aged one month to 6 months) suddenly developed diarrhoea, vomiting, or convulsions, with anaemia and oliguria; they were extremely ill. Investigation revealed uraemia, haemolytic anaemia, thrombocytopenia, and fragmentation of the erythrocytes (burr and triangular forms) in the peripheral blood, but the underlying aetiology was different in each case.

Of the 5 patients, 3 died, and post-mortem examination of 2 showed typical naked-eye and histological changes of acute glomerulonephritis in one and extensive renal cortical necrosis with widespread hyaline thrombi in one. Necropsy was not performed in the third fatal case and the pathogenesis of the erythrocyte defect is unknown. In one of the 2 patients who survived and recovered completely an acute urinary infection appeared to be the aetiological factor, while in the other the syndrome was associated with a raised erythrocyte fragility which returned to normal spontaneously.

The authors suggest that the condition should be regarded as an occasional manifestation of primary renal failure and that all the haematological changes may be a manifestation of acute uraemia in young children. The condition may be commoner than the 18 reported cases would indicate, and in any child with a blood film showing bizarre poikilocytosis and especially burr and triangular cells a full haematological investigation should be carried out and the blood urea level estimated. *A. Ackroyd*

NEOPLASTIC DISEASES

951. **Steroid Therapy in Multiple Myeloma: a Study of Four Cases Treated with Prednisolone**
R. Hume, A. Goldberg, and D. G. Garvie. *Scottish Medical Journal* [*Scot. med. J.*] **6**, 189–196, May, 1961. 3 figs., 27 refs.

Both adrenocortical steroids and corticotrophin have been used in the treatment of multiple myeloma without either agent becoming established as a standard treatment. The authors of this paper have reviewed the published reports and find that of 49 patients so treated, only 17 have shown clinical improvement. Most of these patients were treated for relatively short periods and in doses which in few instances exceeded the equivalent of 60 mg. of prednisolone daily. The present report from the Western Infirmary, Glasgow, deals with 4 patients, 2 of whom received a maximum dose of 60 mg. of prednisolone daily and 2 required doses as high as 150 mg. daily to produce beneficial effects. On these regimens all experienced subjective improvement, including the relief of pain, amelioration of anaemia, and lowering of serum globulin levels. The genesis of the anaemia was studied in 3 of the 4 with both radioactive iron (^{59}Fe) and radioactive chromium (^{51}Cr). Before treatment in all 3 cases the mean erythrocyte life was reduced

and ^{59}Fe utilization was within normal limits. Studies with ^{51}Cr were repeated on 2 of the patients during therapeutic remission, and in both the mean erythrocyte life-span had returned to normal. Further trials of steroid therapy in multiple myeloma are necessary.

A. G. Baikie

952. **A Clinicopathological Study of Benign Hodgkin's Disease**

P. J. DAWSON and C. V. HARRISON. *Journal of Clinical Pathology* [*J. clin. Path.*] **14**, 219–231, May, 1961. 9 figs., 34 refs.

The authors, from the Postgraduate Medical School (Hammersmith Hospital), London, present a detailed clinico-pathological study of 44 cases of benign Hodgkin's disease. The majority of the patients were young adults, and males were affected more often than females, the sex ratio being 2·4:1. Painless enlargement of cervical lymph nodes was the presenting symptom in 36 cases. Naked-eye examination of the nodes obtained by biopsy was not helpful, but reticulin staining of the sections showed loss of the normal glandular structure. In the affected portion of the node there was a notable increase in the proportion of small lymphocytes (to over 75%) and a reduction in the number of reticulum cells. Sternberg–Reed cells were present in varying numbers in all sections.

According to the authors the clinical course of the disease is only slowly progressive and radiotherapy produces long periods of remission. In the series studied treatment was by local excision, radiotherapy, or nitrogen mustard, singly or in combination. The prognosis of the treated cases was fairly good, with a 10-year survival rate of 85%, though 9 cases did progress to classic Hodgkin's disease, with a fatal termination in 7.

J. B. Wilson

953. **The Liver in Hodgkin's Disease**

R. LEVITAN, H. D. DIAMOND, and L. F. CRAVER. *Gut* [*Gut*] **2**, 60–71, March [received May], 1961. Bibliography.

This is a survey of the incidence, morphology, and significance of hepatic changes in Hodgkin's disease, based on a review of the case records of 875 patients with this disease seen at the Memorial Center for Cancer and Allied Diseases, New York, between 1947 and 1957. Of the 875 cases, 300 (34·3%) presented with clinical evidence of liver disease; 112 of these cases came to necropsy and are analysed in this paper. Of the 112 cases, 74 showed diffuse or nodular involvement of the liver with Hodgkin's disease; the remaining 38 all showed some degree of unrelated abnormality of the liver. Only 3 patients (2·8%) in this group died as a consequence of liver failure. An important factor contributing to death was infection (49 cases), but this was considered the primary cause in only 16 cases.

It was impossible to distinguish reliably between disease of the liver due to Hodgkin's disease itself and that due to associated hepatic changes. Massive hepatic enlargement was invariably associated with Hodgkin's disease involving the liver directly; there was no correlation between lesser degrees of hepatomegaly and liver involvement or between hepatomegaly and associated splenomegaly. Diffuse involvement of both lobes of the liver was most common, but the left lobe appeared more extensively involved in cases with associated Hodgkin's disease of the gastro-intestinal tract. Nodular lesions were uncommon and were seen only with granuloma, which was most frequently localized to the portal triads and was not seen invading blood vessels. Hodgkin's sarcoma was found in 21·5% of the entire necropsy series; it tended to involve the liver in a more diffuse manner and frequently invaded the blood vessels.

It is concluded that involvement of the liver by Hodgkin's disease is but one manifestation of a generalized disease process which may occur early or late and carries no prognostic significance for survival.

A. W. H. Foxell

954. **Leukaemia in Childhood and Young Adult Life, Trends in Mortality in Relation to Aetiology**

W. M. COURT BROWN and R. DOLL. *British Medical Journal* [*Brit. med. J.*] **1**, 981–988, April 8, 1961. 17 refs.

In a previous paper (*Brit. med. J.*, 1959, **1**, 1063; *Abstr. Wld Med.*, 1959, **26**, 228) the authors discussed the mortality from leukaemia in England and Wales among adults over the age of 15 years. In the present study the incidence of leukaemia in children and adults up to 30 years of age has been investigated for the period 1911–59; a more detailed analysis has been possible since 1945. The results have also been compared with similar data obtained from the U.S.A. and Japan.

Leukaemia in childhood, particularly the acute lymphoblastic form of the disease, shows a sharp peak at the age of 3 years in both sexes. With the exception of a smaller peak at ages 15 to 19 years, mainly affecting males, there is then a steady decline in incidence to reach a minimum in the quinquennium 25 to 29 years. The childhood peak apparent in Britain since 1921 also occurs in the white population of the U.S.A., but is not seen in Japan or in the non-white U.S. population. While there has been an increase in the number of deaths from leukaemia in the period under survey, some of which is likely to be a real increase, other factors such as better case finding and better classification must be considered. It is pointed out that there has been no sharp change in the incidence of the disease since 1920, and whatever factor caused the change then has not affected the non-white population of the U.S.A. or the Japanese. The adolescent peak has been apparent since 1911, but much more consistently in males than in females; the peak is due to an increased number of cases of a particularly acute form of acute myeloblastic leukaemia. In the first year of life the sex incidence of leukaemia is similar, but thereafter there is a consistently higher incidence in males in Britain, Japan, and in both the white and non-white populations of the U.S.A. Attention is drawn to the high incidence of leukaemia in mongol children, though it is noted that the incidence of the various types of leukaemia affecting them are the same as for other children. Comment is also made upon other genetic factors; leukaemia in both members of a pair of identical twins was found to be very uncommon, only one example occurring among 5,425 deaths in children.

R. B. Thompson

Respiratory System

955. **Dichlorphenamide in Chronic Respiratory Failure**
M. W. McNicol and N. B. Pride. *Lancet* [*Lancet*] **1**, 906–908, April 29, 1961. 1 fig., 11 refs.

Dichlorphenamide is a dichlorinated benzene sulphonamide which acts as an inhibitor of carbonic anhydrase. Studies recently reported have shown that in patients with chronic respiratory failure there is improvement in symptoms and blood-gas tension following administration of the drug. A double-blind cross-over trial of dichlorphenamide was carried out at Hammersmith Hospital, London, on 17 patients with chronic bronchitis and emphysema. Efforts were made to ensure that the condition of the patients was not fluctuating. In all the patients the mixed venous carbon dioxide tension (pCO_2) was 54 mm. Hg or more and the forced expiratory volume in one second ($F.E.V._1$) was less than 0·9 litre. Dichlorphenamide was given in a dosage of 50 mg. 4 times a day for 4 weeks, the first treatment period being followed by 4 weeks without either drug or placebo.

The results were similar to those reported by others. Although there was no consistent alteration in symptoms or signs, the pCO_2 fell in 9 of the 17 patients and there was a small rise in the $F.E.V._1$. Other changes included a fall in venous plasma carbon dioxide content and the plasma potassium level and a small rise in the plasma chloride level. Side-effects were frequent and troublesome and consisted chiefly of headache and gastrointestinal symptoms.

The authors discuss the mode of action of dichlorphenamide; they consider that it may be of value in the treatment of carbon dioxide retention, but this should be shown to exist before treatment is begun.

K. C. Robinson

956. **Noisy Pneumothorax: Observations Based on 24 Cases**
T. Semple and W. M. Lancaster. *British Medical Journal* [*Brit. med. J.*] **1**, 1342–1346, May 13, 1961. 3 figs., 14 refs.

From the Victoria Infirmary, Glasgow, the authors report 24 cases in which Hamman's sounds were heard. These consist in crunching, crackling, or clicking at or near the cardiac apex. Hitherto the sign had been regarded as diagnostic of traumatic or severe spontaneous mediastinal emphysema or, when associated with left chest pain, was considered to be indicative of serious cardiac disease. The 24 patients, of whom 22 were males, were young and apparently healthy. All of them had experienced left-sided chest pain, which was often severe but always abated within a matter of hours. The pain usually preceded the onset of the noise, which was synchronous with the heart beat in addition to varying with respiration; it could often be heard without a stethoscope and was occasionally a cause for complaints by relatives. The only other abnormal physical sign was a slight diminution in breath sounds over the left upper lobe in a few cases. No patient had subcutaneous emphysema, and after the pain had subsided all were symptom-free.

Radiologically, 18 patients had an obvious left apical pneumothorax; 4 other radiographs were initially reported as normal, but further scrutiny with the help of a film taken in full expiration showed a shallow pneumothorax at the left apex. Mediastinal air was never demonstrated. It is emphasized that these pneumothoraces are readily missed, as they are so shallow and are often only apparent on full expiration. It is assumed that the sounds are produced by one or more bubbles of air being moved between the viscous layers of the pleura. Most of the patients were initially suspected of suffering from heart disease, and such diagnoses as myocardial infarction with pericardial friction or pneumopericardium had been made. Previous cases reported in the literature had been variously diagnosed as pericarditis, ruptured heart valve, dissecting aneurysm, or pulmonary embolism. The fact that these patients do not appear ill makes such diagnoses surprising, and it is pointed out that once a case has been seen there is seldom difficulty in recognizing subsequent cases. The condition does not differ from other forms of pneumothorax except for the volume of air in the pleural cavity; "it seems to be the small volume of air leak that is important in producing the noise". When further leakage occurs the characteristic sounds disappear.

The authors conclude that although Hamman's sounds do occur in traumatic and severe mediastinal emphysema, there are many cases where no mediastinal air leak has taken place and only a shallow left pneumothorax exists.

J. Warwick Buckler

LUNGS AND BRONCHI

957. **Changes in the Respiratory Mechanism after Bronchography in Patients with Suppurative Lung Disease.** (Об изменении внешнего дыхения у больных с нагноительнымн процессами в легких под влиянием бронхографии)
A. I. Borohov. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **39**, 77–80, April, 1961.

Changes in the respiratory mechanism were studied 18 to 20 hours after bronchography in 28 men and 8 women, of whom 27 had bronchiectasis, 6 chronic bronchitis, and 3 acute or chronic lung abscess; of the 36 patients, 21 were over 40 years of age. Immediately after the performance of bronchography there was transient giddiness and tachycardia. The immediate fall in oxygen saturation of arterial blood was of short duration and probably of a reflex nature following introduction of the intratracheal tube.

The investigation carried out 18 to 20 hours later showed that bronchography results in an increase of ventilation at rest, mainly by increasing the respiratory rate. Minute volume was increased by 1 to 5 litres in 17 out of 24 patients in whom it was measured, diminished by 1 litre in 2, and remained unchanged in 5. Respiratory rate was increased by 1 to 12 respirations per minute in 15 of 24 patients, diminished by 1 to 5 in 6, and unaltered in 3, while the depth of respiration increased by 40 to 279 ml. in 18 patients, these changes being independent of the nature of the pulmonary lesion. Vital capacity increased in 11 of the 36 patients by 95 to 600 ml., diminished in 12 by 73 to 1,254 ml., and remained unchanged in 13 patients. The increase was particularly conspicuous in 3 patients with severe bilateral bronchiectasis. Maximum pulmonary ventilation increased in 21 patients by up to 15 litres, diminished in 13 by 1·2 to 9 litres, and did not change in one. The increase was noted in all but one of the patients with chronic bronchitis and lung abscess and in half the patients with bronchiectasis. It is suggested that the increased respiratory rate observed many hours after bronchography is probably due to the reflex action of lipiodol on the respiratory centre via pulmonary receptors. The marked reduction in vital capacity and in maximum pulmonary ventilation in patients with bilateral bronchiectasis reflects the profound disturbance of compensatory mechanism, a fact which should be kept in mind whenever bronchography or operative treatment is being considered. *S. W. Waydenfeld*

958. **Combined Therapy: Irradiation and Surgery in the Treatment of Bronchogenic Carcinoma**
F. G. Bloedorn, R. A. Cowley, C. A. Cuccia, and R. Mercado Jr. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **85**, 875–885, May, 1961. 7 figs., 5 refs.

In 1956 a study was begun at the University of Maryland Hospital, Baltimore, the aim of which was to assess the value of preoperative irradiation and radical surgery in the treatment of bronchogenic carcinoma. A preliminary review of the literature revealed that at least 60% of such patients have metastases in the mediastinal lymph nodes and an *en bloc* operation for these nodes is impossible. Further, 15% or more develop metastases in the scalene, supraclavicular, or neck lymph nodes, and these areas also are untouched by surgery. The authors therefore considered that preoperative irradiation might help by sterilizing the mediastinal lymph nodes or, if this was not achieved, by diminishing the vitality and peripheral extension of the primary tumour. The policy adopted for combined therapy and the criteria laid down are fully explained. All cases selected had confirmed operable or inoperable bronchogenic carcinoma localized to one side of the chest, but patients with a malignant pleural effusion and those in whom a biopsy specimen from a lymph-node metastasis in the scalene or supraclavicular area was positive were excluded. Treatment consisted first in teletherapy with ^{60}Co and this was followed by an interval of 2 months before surgery was considered. Details of the teletherapy are given; basically it consisted in delivering 4,000 to 4,500 r. over 4 to 4½ weeks to the primary lesion and adjacent mediastinum, with an additional 1,500 to 2,000 r. to gross tumour.

In assessing the results the patients under study were divided into two groups: (1) those who received their entire treatment at Maryland University Hospital, and (2) those who underwent surgery at other hospitals but received their radiotherapy at the University Hospital. Of the 41 patients in Group 1, only 26 received the full combined therapy; of the remainder, 4 refused surgery and 11 developed distant metastases either during therapy or in the waiting period. Of these 26 patients, 22 were treated by pneumonectomy and 4 by lobectomy. Histological study of this group showed that after cobalt teletherapy the primary site was free of tumour cells in 14 cases (54%) and mediastinal lymph nodes free of metastases in 24 (92%). Of these patients, 12 (50%) are still alive with no evidence of active disease, while the 13th has distant metastases. Among the 16 patients in Group 2 the percentage of inoperable cases, the high percentage of operability after cobalt therapy, and the histological findings in the surgical specimens and lymph-node biopsies were similar to those in Group 1.

The authors realize that the number of patients treated is small and the experience of short duration, but nevertheless they consider that radical irradiation followed by radical surgery is feasible in many patients with bronchogenic carcinoma, and that the results of these preliminary studies are promising. *M. P. Cole*

959. **Cancer of the Lung in Patients with Pulmonary Tuberculosis.** (Рак легкого у больных туберкулезом (По материалам районного диспансера))
S. L. Hejfec. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **39**, 87–91, April, 1961. 17 refs.

The combination of pulmonary tuberculosis with cancer of the lung has been reported to be found in 2 to 30% of tuberculous patients coming to necropsy, but is very rarely recognized during life. During the 8-year period 1952–9 32 cases of lung cancer were discovered among patients attending the Antituberculosis Dispensary No. 12, Leningrad, representing an incidence of 0·45%. The diagnosis was made in 5 out-patients and 27 in-patients (in 9 of the latter during life and in 18 at necropsy).

Of the 28 male and 4 female patients forming the series, 2 were aged 31 to 40 years, 7 aged 41 to 50, 11 aged 51 to 60, and 12 were over 60. The lung tumour was primary in 28 cases (central in 24 and peripheral in 4) and metastatic in 4 (from the stomach in 2, the oesophagus in 1, and the uterus in 1). The growth was situated in the right lung in 27 cases (in the upper, middle, and lower lobe in 15, 1, and 11 cases respectively) and in the left lung in 5 cases (upper lobe 4 and lower lobe 1). All metastatic tumours were in the lower lobes; in 20 patients both the tuberculous and the malignant lesion were in the same lobe. Neoplasia was associated with the following types of tuberculosis: focal in 5 cases, infiltrative in 4, disseminated in 8, and fibrocavernous in 13. The sputum of 11 patients had been constantly positive

and of a further 5 patients intermittently positive for tubercle bacilli. At the time the cancer was diagnosed 15 patients had been under observation for 1 to 3 years, 12 for 3 to 6 years, 3 for 7 years, one for 14 years, and one for 23 years.

Retrospective analysis of the case histories of these patients showed that in at least 10 of them there was a period when the discrepancy between improvement in the clinical and radiological signs and the poor subjective condition of the patient was overlooked or not given its due significance. Recognition of cancer of the lung in a tuberculous patient is one of the most difficult clinical problems. Suspicion should arise, however, when some alteration takes place in the pattern of the course of the disease, especially if an exacerbation does not run the usual clinical course characteristic of the patient in question. In 19 of the cases in this series one of the following warning signs was noted at a definite period of the disease: (1) some symptom (most often pain and next in frequency cough) became much more prominent than it had been previously (9 cases); (2) there was unusually sudden replacement of one set of prominent symptoms by another (6 cases); and (3) dissociation of symptoms, that is, one or more symptoms became more prominent and others diminished or disappeared (4 cases). *S. W. Waydenfeld*

960. **Evaluation of Technique and Results for Obtaining Sputum for Lung Carcinoma Screening: a Study by Blind Technique**

L. Leilop, M. Garret, and H. A. Lyons. *American Review of Respiratory Diseases* [*Amer. Rev. resp. Dis.*] 83, 803–807, June, 1961. 4 refs.

An evaluation of the heated aerosol technique for the collection of sputum for the cytological diagnosis of cancer of the lung is reported from the State University of New York Downstate Medical Center and King's County Hospital Center, Brooklyn, New York. Data for the study were derived from a survey designed to assess the relative merits of symptoms, x-ray examinations of the chest, and cytological studies of sputum for screening population groups for the early diagnosis of lung cancer. The method tested was based on the following premises: (1) hypertonic solutions in contact with the bronchial mucosa stimulate the secretion of sputum; (2) a warm solution reduces irritation produced by hypertonicity; (3) a solution is best administered as an aerosol mist with particle size of 1 to 10 μ; and (4) the addition of propylene glycol forms a stable and evenly distributed mist on the bronchial mucosa.

A total of 500 specimens of sputum were obtained from 205 subjects: 96 specimens from apparently healthy subjects, 349 from patients with various respiratory diseases, and 55 from patients with suspected malignant disease of the respiratory tract. A visible aerosol, delivered from a special nebulizer which maintained solutions at 108° to 110° F. (42·2° to 43·4° C.), was inhaled for at least 20 minutes. Three different solutions were used: (1) propylene glycol and hypertonic saline; (2) tap water; and (3) normal saline. Specimens were also obtained by postural drainage alone for at least 20 minutes. All sputum was expectorated directly into sterile jars containing 70% alcohol and sent within a few hours to the laboratory, where a blind technique for examination was employed. Specimens were not centrifuged. Smears were prepared and stained by the routine Papanicolaou technique and the original Papanicolaou classification was used.

The solution of propylene glycol and hypertonic saline provided the best specimens for cytology, with 88·3% satisfactory specimens compared with 66·6% resulting from the use of the other agents. No false positive results were obtained, and malignancy was diagnosed in every one of the 9 cases subsequently proved neoplastic by other means (biopsy or necropsy). Postural drainage was regarded as unsatisfactory, since false positive results (that is, cells simulating neoplasia) are said to have been yielded by this method.

Because the aerosol technique is simple and gives a high percentage of satisfactory specimens for examination in the authors' hands they suggest it should be considered where the screening of large populations for pulmonary malignancy is undertaken. Adverse effects of the aerosol appear to be limited to occasional slight irritation of mouth and throat. *W. Raymond Parkes*

961. **Polycythaemia in Emphysema**

D. B. Shaw and T. Simpson. *Quarterly Journal of Medicine* [*Quart. J. Med.*] 30, 135–152, April, 1961. 6 figs., bibliography.

In an investigation undertaken at Chase Farm Hospital, Enfield, and the Postgraduate Medical School of London in an attempt to discover the reason for the rarity of polycythaemia in hypoxic emphysematous patients 36 emphysematous patients with bronchitis and dyspnoea were studied; in 33 of them the arterial oxygen saturation was below 92% and these patients were designated the hypoxic group, the remaining 3 being regarded as controls.

The erythrocyte count, haemoglobin and haematocrit values, and mean corpuscular haemoglobin concentration (M.C.H.C.) were the same in the two groups, but the mean erythrocyte volume (measured by means of radioactive chromium) and the plasma volume were greater in the hypoxic group. In 33 cases erythropoietic activity was estimated by the radioactive-iron technique and the effects of the oral administration of ferrous sulphate on the plasma iron level, plasma iron-binding capacity, and erythrocyte survival time were determined in 17, 11, and 8 patients respectively.

It was found that in the hypoxic patients chronic bronchial infection caused an average increase in erythrocyte production of 40%. The mean erythrocyte half-life was found to be reduced in only one of the 8 patients in whom it was measured. The authors suggest that emphysematous patients respond to hypoxia by increased erythropoiesis. However, this is masked in the erythrocyte count and haematocrit value by a parallel rise in plasma volume. Thus polycythaemia is not rare in emphysema, but is only revealed if judged by the criterion of the total erythrocyte volume rather than the peripheral blood count. *D. Goldman*

Endocrinology

THYROID GLAND

962. **Cretinism and Taste Sensitivity to Phenylthiocarbamide**
G. R. FRASER. *Lancet* [*Lancet*] **1**, 964–965, May 6, 1961. 11 refs.

The normal proportion of non-tasters of phenylthiocarbamide (PTC) in the general population is about 30%. The taste response to PTC is known to be mediated by a single allelic pair of genes. A connexion between this response and thyroid disease was suggested by Harris *et al.* (*Lancet*, 1949, **2**, 1038) and confirmed by Kitchin *et al.* (*Brit. med. J.*, 1959, **1**, 1069; *Abstr. Wld Med.*, 1959, **26**, 298), who found a gross excess of non-tasters among males with non-toxic goitre. Of 17 children with athyreotic cretinism tested by the author at the Birmingham Children's and United Oxford Hospitals, 15 were non-tasters. Of 33 parents of these children, 18 (55%) were non-tasters. If the proportion of non-tasters among the cretins is taken as 88% it would be expected that that among the parents would be 50%. No hearing defects were found in the athyreotic children. Presumably, therefore, their defect was not in the incorporation of iodide into organic form, which is thought to be the cause of the syndrome of deafness with euthyroid goitre. Of 10 non-athyreotic cretins, 5 were tasters, 4 were non-tasters, and one could not be tested; these results do not deviate significantly from expectation. Of 13 parents of 15 non-athyreotic cretin children, only 5 were non-tasters, a normal proportion.

The distinction between tasters and non-tasters of PTC may be connected with changes in the metabolism and disposal of antithyroid substances. This mechanism may be defective in non-tasters, leading to eythyroid goitre or destruction of the thyroid gland.

[The age and sex of the 17 athyreotic and of the 15 non-athyreotic children are not given so that comparison with the findings of Kitchin *et al.* is inaccurate.]

G. de M. Rudolf

963. **Incidence and Aetiology of Thyroid Carcinoma**
J. WILLIS. *British Medical Journal* [*Brit. med. J.*] **1**, 1646–1649, June 10, 1961. 49 refs.

The incidence of thyroid cancer as a cause of death in necropsy and surgical material and its association with the various types of surgically treated goitre have been calculated.

Potential aetiological agents have been discussed and the following conclusions formulated: (1) Thyroid carcinoma is a rare finding at necropsy. (2) The incidence of carcinoma in specimens available for histological examination in this series is 4·1%. (3) Malignant change is more often associated with non-toxic nodular goitre than with toxic nodular goitre. (4) The diagnosis of thyrotoxicosis does not exclude the possibility of malignancy. (5) The frequency with which thyroid cancer is being diagnosed in surgical material is increasing. This is due to an increase in the total number of operations and to an increase in the number of operations for nodular goitre. (6) The use of antithyroid drugs in Northern Ireland does not appear to have influenced the increase of thyroid cancer. (7) The data at present available appear to give no indication that the adult thyroid gland is susceptible to radiation cancer.—[Author's summary.]

964. **Thyroid Suppressibility after Therapy for Thyrotoxicosis**
I. B. HALES, J. MYHILL, T. H. ODDIE, and F. F. RUNDLE. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **21**, 569–574, May, 1961. 13 refs.

At the Royal North Shore Hospital, Sydney, Australia, 76 patients were studied by means of thyroid suppression tests, using thyroxine or triiodothyronine, at various intervals after treatment with radioactive iodine. It was shown that suppressibility returned in proportion to the effectiveness of treatment and the observed clinical improvement. In 3 patients who were judged clinically to be euthyroid the results of the suppression tests were in the thyrotoxic range and later 2 of them became clinically thyrotoxic and required further treatment. Significant suppression of thyroid function by these drugs could be shown to occur as early as 6 weeks after treatment.

M. C. G. Israëls

965. **Effect of D-Thyroxine on Thyrotoxicosis and on the Associated Exophthalmos**
W. D. ALEXANDER, D. A. KOUTRAS, W. W. BUCHANAN, and J. CROOKS. *British Medical Journal* [*Brit. med. J.*] **1**, 1194–1195, April 29, 1961. 1 fig., 7 refs.

It has been suggested that while D-thyroxine has considerably less calorigenic effect than L-thyroxine, it retains the other actions of the natural hormone. Some confirmation of this has been provided by reports of suppression of thyroid function by D-thyroxine in both normal and hyperthyroid patients owing, it was assumed, to inhibition of thyrotrophin production.

This paper from the Gardiner Institute, Western Infirmary, Glasgow, reports a controlled study of the effects of D-thyroxine in hyperthyroidism. Of 8 thyrotoxic patients treated with either 1 mg. or 4 mg. of D-thyroxine daily for 12 weeks, none showed any significant gain in weight or other clinical evidence of improvement. Nevertheless, fortnightly estimates of the 2½-hour uptake of ^{132}I by the thyroid gland showed a progressive fall which was greater in those receiving the larger dose. There were, however, associated increases in the plasma inorganic iodine level and in the absolute iodine uptake (calculated as the product of thyroidal clearance of iodine and the plasma inorganic iodine level). The reduced uptake of ^{132}I therefore represented not a reduction in

thyroid function but an increase in the extrathyroidal iodine pool. This was thought to be due to the liberation of part of the iodine content of the D-thyroxine. Similar changes, although of greater degree, were seen in a control group of 6 thyrotoxic patients treated for the same period with potassium iodide in doses providing amounts of iodine equivalent to those in the D-thyroxine-treated group.

A further group of 19 hyperthyroid patients were treated with methylthiouracil until they became euthyroid, during which time regular measurements of the degree of exophthalmos were made. Seven of these patients also received 4 mg. of D-thyroxine daily in addition, the remaining 12 given methylthiouracil only serving as controls. There was no significant difference in the degree of exophthalmos between the two groups, all except 3 members of which showed some increase in proptosis.

The authors conclude that in the doses used in this study D-thyroxine is of no value in the treatment of thyrotoxicosis or the associated exophthalmos.

H.-J. B. Galbraith

966. **Aplastic Anaemia Due to Treatment with Potassium Perchlorate**

Q. J. G. Hobson. *British Medical Journal* [*Brit. med. J.*] 1, 1368–1369, May 13, 1961. 8 refs.

The author, from the West Middlesex Hospital, London, describes a fatal case of aplastic anaemia due almost certainly to perchlorate therapy. The patient, a woman aged 50, had been treated for thyrotoxicosis by partial thyroidectomy at the age of 38. Three years before death polyarthralgia and symptoms suggesting a recurrence of hyperthyroidism had appeared. Nine months before death she was found to have clinical and laboratory evidence of both hyperthyroidism and rheumatoid arthritis, investigations including a radioactive iodine study. Treatment for these two conditions was begun with potassium perchlorate (200 mg. 4 times daily) and prednisolone respectively. The daily dosage of perchlorate was reduced to 600 mg. after 14 weeks as signs of hypothyroidism had developed; triiodothyronine, 0·06 mg. daily, was started at the same time and continued for 12 weeks.

After 32½ weeks of antithyroid treatment purpura appeared, but the patient did not report to the hospital until epistaxis occurred one week later. She was then febrile and had panhaematocytopenia. Sternal marrow examination showed a complete absence of erythropoietic and granulopoietic cells and of megakaryocytes. In spite of treatment with antibiotics, fresh-blood transfusion, and corticosteroids she died 5 days later with slight jaundice, a haemorrhagic state, and severe pneumonia.

The author has met no other serious toxic effects in about 50 patients treated with perchlorate alone. However, one woman aged 48 with very severe hyperthyroidism occurring 20 years after thyroidectomy for thyrotoxicosis developed agranulocytosis after 30 days' treatment with carbimazole, 45 mg. daily, combined with perchlorate, 600 mg. daily. This patient recovered.

H.-J. B. Galbraith

967. **Fatal Aplastic Anaemia after Treatment of Thyrotoxicosis with Potassium Perchlorate**

R. S. Johnson and W. G. Moore. *British Medical Journal* [*Brit. med. J.*] 1, 1369–1371, May 13, 1961. 1 fig., 11 refs.

A woman aged 29 presented at Southend General Hospital with hyperthyroidism. After the clinical diagnosis had been confirmed by radioactive iodine studies, treatment was started with 1,000 mg. of perchlorate daily. At the end of 3 months the appearance of mild hypothyroidism prompted the reduction of dosage to 600 mg. daily. One month later she was found to be grossly anaemic, the haemoglobin level being 5 g. per 100 ml., platelet count 29,000 per c.mm., and leucocyte count 6,000 per c.mm. (neutrophils 38%). Bone-marrow examination showed a hyperplastic marrow with evidence of maturation arrest. Within a week severe neutropenia appeared, and this was soon followed by pathological bleeding. In spite of repeated blood transfusions and large doses of corticosteroids and antibiotics the patient died within 6 weeks of admission. Post-mortem examination showed a complete aplasia of the bone marrow, multiple haemorrhages, and septicaemia (thought to account for the jaundice which had developed terminally).

In their discussion the authors analyse the toxic effects described in the literature as occurring in 818 cases treated with potassium perchlorate. The total incidence was 4%. The commonest reactions were rashes, alimentary disturbances, fever, and sore throat; lymphadenopathy and neutropenia were less common. Two cases of severe neutropenia, one case of agranulocytosis, and one of agranulocytosis with thrombocytopenia have been described. The last 2 patients recovered. Toxic effects were several times more frequent when daily doses of 1,200 mg. or more had been used. All the severe haematological reactions occurred with doses of 1,000 mg. or more.

H.-J. B. Galbraith

968. **Kidney Function in Various Thyroid States**

R. V. Ford, J. C. Owens, G. W. Curd Jr., J. H. Moyer, and C. L. Spurr. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] 21, 548–553, May, 1961. 10 refs.

Renal function was studied at the Veterans Administration Hospital, Houston, Texas, by determining the glomerular filtration rate (inulin clearance), the renal plasma flow (PAH clearance), and the tubular excretory capacity for PAH in 7 patients with hyperthyroidism (2 treated by thyroidectomy and 5 with radioactive iodine), 3 with primary hypothyroidism, 3 with glomerulonephritis, 4 with a low basal metabolic rate because of hypopituitary states, and also in 3 normal subjects. The renal excretory function was studied both before and after administration of triiodothyronine, and 2 of the normal subjects were also given thyroxine. The results, which are tabulated, suggest that renal tubular capacity is most affected in primary and secondary hypothyroidism and is restored by treatment with triiodothyronine, but that this substance has no effect on euthryoid patients.

M. C. G. Israëls

DIABETES MELLITUS

969. **Blood Lipids, Mucoproteins, and Fibrinolytic Activity in Diabetic Indians and Africans in Natal: Possible Relation to Vascular Complications**
M. HATHORN, T. GILLMAN, and G. D. CAMPBELL. *Lancet* [*Lancet*] **1**, 1314–1318, June 17, 1961. 41 refs.

In this paper from the University of Natal and King Edward VIII Hospital, Durban, the clinical aspects of diabetes in Africans and Indians in Natal are first briefly reviewed and the low incidence of vascular complications in diabetic Africans and their high incidence in diabetic Indians, as shown by the findings of a study of 133 Africans (Zulus) and 207 Indians with the disease, emphasized. To examine the biochemical characteristics of diabetes in these two racial groups 178 patients (96 Indian, 82 African) were selected at random from among those attending a diabetic clinic, blood samples taken, and determinations made of the euglobulin lysis time and plasma fibrin, blood glucose, and serum total lipid, cholesterol, and mucoprotein concentrations. Control estimations were made on 101 subjects (41 Indian, 60 African) drawn from the domestic staff of the hospital.

The mean euglobulin lysis times were significantly longer in Indian diabetics of both sexes than in their African counterparts, thus indicating decreased fibrinolytic activity. The mean plasma fibrin levels in Indian and African male diabetics and in African female diabetics were all significantly higher than in the corresponding control groups and all values, both for diabetics and controls, were higher than corresponding values recorded for Europeans. The mean serum total lipid content was significantly raised in Indian diabetics, this being particularly marked in the female patients. The only significant difference found in the serum cholesterol values was that between Indian and African diabetic males, the mean value in the former being higher than in the latter, though still much lower than in European diabetics. The serum cholesterol and total lipid values found among the African diabetics would be regarded as within the normal range for Europeans. Indian diabetics with high serum total lipid values also showed prolonged euglobulin lysis times and high serum cholesterol levels. The findings support the concept that the plasma fibrinolytic system is of importance in preventing mural thrombosis and coronary occlusion. No support was found for the idea that the serum mucoprotein level is of importance in the development of atherosclerosis.

It is suggested that the diabetes seen in Indians is reminiscent of the syndrome of " steroid diabetes " and that hormones, particularly sex hormones, may play a significant part in the high incidence of vascular complications seen in these patients. *F. W. Chattaway*

970. **Birthweight of Children of Diabetic Fathers**
T. D. KELLOCK. *Lancet* [*Lancet*] **1**, 1252–1254, June 10, 1961. 1 fig., 4 refs.

The author of this paper from the Central Middlesex Hospital, London, compared the birth weights of children of 117 diabetic fathers with those of the children of 117 non-diabetic fathers. The diabetics were attending the hospital diabetic clinic and the control subjects, matched for age by decades, were selected from outpatients attending other clinics.

The men in the two groups were asked to state the birth weights of their children and, despite many vague and imprecise answers, the following facts emerged. The diabetic fathers had 161 children, of whom the birth weights of 27 were unknown; 17 children weighed 9 lb. (4·08 kg.), 7 weighed 10 lb. (4·536 kg.), and 5 weighed more than 10 lb. at birth. The control patients had 200 children, of whom 20 had unknown birth weights, while 9 weighed 9 lb., 4 weighed 10 lb., and none weighed more than 10 lb. at birth. The diabetic fathers weighed more than the controls, but no correlation could be discovered between the body weight of the father and the birth weight of the child. One diabetic father had a diabetic wife, but no wife of a control father was known to be diabetic. The author concludes that diabetic fathers have a tendency to produce heavier babies than non-diabetic fathers. *Charles Rolland*

971. **Prevalence of Diabetes in Women Thirteen Years after Bearing a Big Baby**
M. G. FITZGERALD, J. M. MALINS, and D. J. O'SULLIVAN. *Lancet* [*Lancet*] **1**, 1250–1252, June 10, 1961. 25 refs.

Of the 21,940 babies born alive in Birmingham in 1947, 134, or 0·6%, weighed over 10½ lb. (4·762 kg.) at birth. Thirteen years later 71 mothers of these large babies were traced and 61 cooperated in an investigation at the General Hospital, Birmingham, of the prevalence of diabetes among them. These 61 mothers were given 50-g. oral glucose tolerance tests after an overnight fast, blood glucose being estimated in capillary blood taken before and at 30-minute intervals after the glucose was administered.

It was found that 20 of the women had abnormal glucose tolerance. Of these, 10 had definite diabetes. Only one of them had been known to have the disease and 3 others had mild symptoms suggestive of diabetes of recent onset. The remaining 10 gave results which were interpreted as showing probable diabetes. The mean age of the 20 women with abnormal glucose tolerance was 49·9 years and of the 41 with normal tolerance 43·6 years—a significant difference. Glucose tolerance was normal in all the women under the age of 40 years, and abnormal in 65% of those aged 50 years or more.

Compared with the mean weight of married women in Birmingham who had borne 3 children (Lowe and Gibson, *Brit. med. J.*, 1955, **2**, 1006; *Abstr. Wld Med.*, 1956, **19**, 320) 40% of the 61 women in the present study were obese, but there was no significant difference between the mean body weight (166·0 lb., or 75·296 kg.) of the 41 women with normal glucose tolerance and that (169·5 lb., or 76·885 kg.) of the 20 with abnormal tolerance. The 61 women had a total of 326 children, but when allowance was made for age there was no significant difference between the parity of those with normal and those with abnormal glucose tolerance. A family history of diabetes in relatives of the first or second degree was given by 37% of the women with normal glucose tolerance, but curiously enough by only 15% of those with abnormal results.

The authors stress that the birth of a big baby can rarely be isolated from obesity, multiparity, and a family history of diabetes. The separate significance of giving birth to a large child as a possible aetiological factor in diabetes requires further study. *Charles Rolland*

972. **Dimethyldiguanide in the Treatment of Diabetic Children**
A. W. FERGUSON, P. L. DE LA HARPE, and J. W. FARQUHAR. *Lancet* [*Lancet*] **1**, 1367–1369, June 24, 1961. 2 figs., 7 refs.

In this double-blind trial dimethyldiguanide metformin reduced glycosuria in most of the diabetic children treated, and on its withdrawal their glycosuria became temporarily more severe. Insulin remained necessary in all, and, although reductions of up to 42% were achieved, these reductions were not offset by enhanced stability of control, and indeed use of the drug was associated with disadvantageous side-effects in most of the children.

Under the rigid conditions of this limited trial the drug offered no advantage to the diabetic child. On the contrary it complicated control by adding yet a further variable to such others as diet, insulin, exercise, mood, and co-operation by parent or child.—[Authors' conclusions.]

973. **Oral Hypoglycemic Therapy. Long-term Results in Older Diabetic Patients**
T. A. SKILLMAN, G. J. HAMWI, H. DRISKILL, and M. H. PENROSE. *Geriatrics* [*Geriatrics*] **16**, 209–217, May, 1961. 7 figs., 9 refs.

The effects of long-term administration of hypoglycaemic drugs by mouth in older diabetics were studied in 125 patients, all over 60 years of age, attending the Ohio State University Diabetic Clinic, Columbus. The patients, whose diabetes could not be controlled except with insulin, received either tolbutamide in a dosage of 1 to 2 g. daily or chlorpropamide in a dosage of 0·1 to 0·5 g. daily and were observed for 3 to 48 months. A primary response was judged to be one in which the fasting or postprandial blood sugar level fell to 150 mg. per 100 ml. or less within 30 days; when no such conversion occurred the case was considered to be one of primary failure. In some cases there was a primary response but later the blood sugar level rose; this was designated a secondary failure. Of 80 patients given tolbutamide, 50 gave a primary response, but in at least 10 of these there was secondary failure within a year; after 2 years' treatment the percentage of secondary failures was 2·5 a month.

Of 70 patients given chlorpropamide, 40 showed a primary response, and in 37 of these the diabetes was still controlled at the end of a year; after 2 years' treatment the secondary failure rate was 1% per month. No conclusions could be drawn concerning the relationship between age, sex, and weight of the patients and the response. Symptoms suggestive of hypoglycaemia were seen in 4 out of the 80 patients given tolbutamide and in 3 of the 70 given chlorpropamide, and a rash was observed in 3 patients receiving tolbutamide and in one given chlorpropamide. In all the long-term treated patients there was a slight tendency to an increased serum cholesterol level. About one-third of the patients who failed to respond to tolbutamide later responded to chlorpropamide. *J. N. Agate*

974. **Hypophyseal-stalk Section in the Treatment of Advancing Diabetic Retinopathy: Report of Three Cases**
R. A. FIELD, W. A. HALL, J. S. CONTRERAS, and W. H. SWEET. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 689–698, April 6, 1961. 11 figs., 10 refs.

The results are reported of division of the hypophyseal stalk for amelioration of advancing diabetic retinopathy in 3 patients seen at the Massachusetts General Hospital and the Massachusetts Eye and Ear Infirmary, Boston. The patients were carefully selected after investigation had shown progressive loss of vision in spite of meticulous medical control of the diabetes and the absence of very severe renal or cardiovascular disease. There was, however, some renal damage as shown by the presence of albuminuria in all 3 patients and intercapillary glomerulosclerosis in the 2 on whom a renal biopsy was performed. Careful maps were made of the fundi before and after operation and these together with coloured illustrations of the fundi are reproduced. The patients were followed up for 18, 5, and 4 months respectively. (In a footnote it is stated that 6 further patients have been operated on, one of whom died shortly after the operation.)

The most striking results were the complete cessation of haemorrhagic disease and the disappearance of neovascularization. In addition there was rapid clearing of the turbid vitreous which is seen in most patients with diabetic retinopathy. The expected signs and symptoms of anterior pituitary insufficiency developed in all cases, but with the exception of corticosteroids no hormones were given unless the symptoms became a real hardship to the patient. Insulin requirements fell in all cases, but not as dramatically as has been reported by other workers.

[These cases, while few in number, are so well documented that all those interested in the subject should read the original paper in full.] *T. D. Kellock*

975. **Hypercholesterolaemia and Diabetes Mellitus**
J. N. HARRIS-JONES and D. J. WARD. *Journal of Clinical Pathology* [*J. clin. Path.*] **14**, 279–282, May, 1961. 4 figs., 11 refs.

From the General Hospital, Llanelly, and the Royal Hospital, Sheffield, 2 cases are described in which hypercholesterolaemia secondary to acute diabetes mellitus was abolished, the serum cholesterol level being restored to normal, with control of the diabetes by insulin. In contrast, 2 further cases are presented in which essential hypercholesterolaemia was present in association with, but independent of, diabetes mellitus; in these cases control of the diabetes did not affect the blood cholesterol level. The results of a study of the blood glucose and serum cholesterol levels in families with essential hypercholesterolaemia suggested that impaired carbohydrate tolerance is not a feature of this type of hypercholesterolaemia. *F. W. Chattaway*

The Rheumatic Diseases

976. **Zoxazolamine in the Treatment of Gout.** (La zoxazolamine dans le traitement de la goutte)
H. SERRE, L. SIMON, and A. CIURANA. *Revue du rhumatisme et des maladies ostéo-articulaires* [*Rev. Rhum.*] **28**, 226–233, May, 1961. 6 figs., 18 refs.

This article from the Rheumatological Clinic, Montpellier, describes the use of zoxazolamine in the treatment of 27 cases of gout. In most cases the drug was given in doses gradually increasing up to 600 mg. a day, and daily blood and urine urate estimations were made so long as the patient was in hospital. Twelve patients admitted for other conditions were similarly treated for control purposes.

It was found that administration of the drug caused a reduction in blood urate level to normal and an increase in urate excretion in all the gouty subjects except one whose blood urate level before treatment was normal. In the control subjects, whose blood urate levels were also normal, the reduction under treatment was much less marked. In 2 gouty cases an appreciable reduction in the size of tophi was noted after 8 months of treatment. No side-effects of any significance were noted. Acute gouty attacks occurred in 6 cases during the early phase of treatment and in 2 of these the drug had to be withheld. Renal colic occurred in 3 cases after high dosage. Aspirin was shown to have an antagonistic effect on the uricosuric action of zoxazolamine, but other uricosuric agents, such as phenylbutazone, probenecid, and "G 28315" [a phenylbutazone derivative], did not have this effect and can therefore be used in association with zoxazolamine with advantage: they may have a synergistic effect.

The authors conclude that zoxazolamine is a powerful uricosuric agent, of value in the treatment of chronic gout. Its effectiveness may lead to severe acute attacks at the beginning of treatment and for this reason dosage should be increased only gradually. *B. E. W. Mace*

RHEUMATIC FEVER

977. **Bed Rest, Salicylates, and Steroid in Rheumatic Fever**
E. G. L. BYWATERS and G. T. THOMAS. *British Medical Journal* [*Brit. med. J.*] **1**, 1628–1634, June 10, 1961. 5 figs., 15 refs.

The course of rheumatic fever in hospital in patients treated by bed rest alone and not given prophylaxis has been studied, and the degree of carditis related to other features of the attack. Prolonged raised temperature and sedimentation rate were more closely related to carditis than the sleeping pulse, but in severe attacks persistent tachycardia was a constant feature and carried a poor prognosis. Anaemia and loss of weight were uncommon and occurred only in the worst cases. Nodules were rare without heart disease, but were present in a quarter of those with slight carditis and in half of those with severe carditis.

The course in hospital in some patients treated by bed rest has been compared with that in others who were given 6-week courses of A.C.T.H., cortisone, or aspirin, together with prophylactic sulphonamide. The two groups were comparable in most respects, although (*a*) they were not run concurrently; (*b*) only the drug-treated series was given prophylaxis; and (*c*) the latter had less heart disease at the start. Arthritis, temperature, and sedimentation rate subsided more slowly in the bed-rest series, but the temperature was similar in the two by the fourth week, arthritis by the sixth week, and the sedimentation rate by the eighth week; the rapid subsidence of activity in some of the bed-rest cases was striking. There was little difference in changes in cardiac status in the two groups, except in the development or disappearance of soft (grade 1–2) murmurs, and this may have no important effect on the residual heart state 5 years later.

A third group of 47 cases was treated with 12-week courses of either cortisone or salicylate and did no better than those who had salicylate, cortisone, or A.C.T.H. for only 6 weeks.

Conclusions are drawn on the role of bed rest, salicylate, and steroid in the management of the disease. In many cases bed rest with salicylates to control fever and joint pain suffices, but in a few with severe attacks and cardiac enlargement delta-steroids are indicated and salicylates are potentially dangerous since they predispose to pulmonary complications.—[Authors' summary.]

978. **Correlation of Population Age with Recovery Rates of β-Hemolytic Streptococci and Serological Responses: Relationship to Rheumatic Fever**
M. M. STREITFELD and M. S. SASLAW. *Journal of Infectious Diseases* [*J. infect. Dis.*] **108**, 270–277, May–June, 1961. 1 fig., 18 refs.

In this investigation reported from the University of Miami School of Medicine, Florida, the recovery rate of β-haemolytic streptococci from throat cultures and the serological responses to these organisms were studied in three different age groups of apparently healthy subjects —800 elementary school children aged 6 to 9 years, 801 junior high school children aged 12 to 15 years, and 1,815 adults. Throat swabs were taken from all subjects and samples of blood from the adults. Streptococcal isolation rates were found to vary inversely with age. Group-A β-haemolytic streptococci were isolated from 14·4% of the children aged 6 to 9 years, from 7·9% of those aged 12 to 15, and from 2·2% of the adults. The pattern was similar for isolation of other β-haemolytic streptococci. There was no significant seasonal fluctuation. Group-C and Group-G β-haemolytic streptococci were found to

be far commoner in the throats of children than in those of adults.

The average serum antistreptolysin-O (ASO) titre in the adults was between 71 and 74, but in those whose throat swabs were positive the average titre was 115 to 146. In an earlier study of other groups of children in Miami the average ASO titre was found to be approximately 100. The lower average ASO titre in adults was considered to be due to a higher streptococcal carrier rate in the children. These results generally parallel the higher incidence of acute rheumatic fever in children.

John Lorber

CHRONIC RHEUMATISM

979. **Psoriasis and Arthritis: Clinopathologic Study**
W. B. Reed, S. W. Becker, R. Rohde, and C. L. Heiskell. *Archives of Dermatology* [*Arch. Derm.*] **83**, 541–548, April, 1961. 2 figs., 17 refs.

The clinical features in 86 cases of arthritis associated with psoriasis and the post-mortem findings in 16 of them are discussed in this paper from the University of Southern California School of Medicine, Los Angeles. Of the 16 deaths, 2 were due to perforated peptic ulcer and one to coronary thrombosis, although a penetrating peptic ulcer was also present. Myocardial infarction was responsible for 4 further deaths, infection (pyelonephritis, bronchopneumonia, and septicaemia) for 3, haemorrhage (pulmonary and oesophageal varices) for 2, and adrenal insufficiency, secondary amyloidosis, suicide (in a patient with a steroid-induced psychosis), and perforation of the terminal ileum from aminopterin for one each. Steroids were being administered to 8 of the 16 patients at the time of death and complications from this led to peptic perforation, psychosis, uncontrolled staphylococcal infection, increased hypertension, and acute adrenal insufficiency. All the patients continued to have exfoliative psoriasis in spite of a high dosage of steroids.

Discussing complications in the series as a whole the authors state that of the 86 patients, peptic ulcers developed in 10, osteoporosis in 2, and active tuberculosis in 2. One gained 100 lb. (45·35 kg.) in weight in a year. Triamcinolone caused the greatest number of complications; during treatment with this drug diabetes mellitus developed in one patient, muscular weakness in 3, and in one there was rupture of a pregnant uterus. The psoriasis exfoliated in 5 patients while they were receiving triamcinolone.

Electrocardiographic examination, which was carried out on 84 of the 86 patients, revealed abnormalities in 14 patients under 50 years of age and in 22 of those over 50. Spondylitic heart disease was present in 3 patients and strongly suspected in 2 others. These patients apparently had more severe systemic disease, with iritis, urethritis, severe peripheral arthritis, and pustular psoriasis.

[The cases of spondylitis, pustular psoriasis, iritis, and urethritis would probably have been classified in Britain as cases of Reiter's disease; they indicate once more the possible interrelationship between this condition, psoriasis, and arthritis.] *Benjamin Schwartz*

980. **Oxyphenbutazone ("Tanderil", G 27202): an Antirheumatic Derivative of Phenylbutazone**
M. Kelly. *Medical Journal of Australia* [*Med. J. Aust.*] **1**, 851–853, June 10, 1961. 17 refs.

Phenylbutazone has proved useful in the treatment of rheumatic disorders and toxic effects appear to be uncommon provided the dosage does not exceed 400 mg. a day and if it is not given to aged patients or those with dyspepsia or cardiac disease. Nevertheless, side-effects do occur from time to time and in the search for a non-toxic derivative with the same antirheumatic action two substances of interest have been synthesized, both of which are metabolites of phenylbutazone. One of these, oxyphenbutazone (G 27202; "tanderil"), has been found to have, like phenylbutazone, antirheumatic properties, its effect on the inflammation of acute gout being especially striking, although it has no effect on the excretion of uric acid. The other drug, G 28315, has no clinical effect on acute gout, but it is powerfully uricosuric.

The purpose of the present communication is to record the author's clinical observations with tanderil. He considers that its effect is so striking that rigidly controlled trials are unnecessary. In a daily dosage of 300 mg. he found the substance to be less toxic, but also less effective, than phenylbutazone. A dosage of 800 mg. daily for 3 consecutive days in every 6 was tried in 43 cases—13 of rheumatoid arthritis, 2 of osteoarthritis, 17 of local fibrositis, and 11 of multiple fibrositis. Patients reported by telephone on their rheumatic symptoms and general well-being. In more than one-half of the group the effect was "striking" and in one-quarter it was as good as that of phenylbutazone. Nine patients reported toxic effects. A dosage of 600 mg. daily for 5 days of each week was tried on 50 patients suffering from similar disorders. A rather smaller proportion gave a "striking" response than with the 800-mg. dosage, but toxic symptoms occurred in only 6 cases.

[The author's reasons for not accepting the need for a controlled therapeutic trial are not convincing. His figures purporting to show a difference in toxic effects and in the proportion showing "striking" improvement between the 600-mg. and 800-mg. dosage schemes are not statistically significant.] *Kenneth Stone*

981. **A Latex Fixation Test Using British Latex and Bovine Gamma Globulin**
R. B. Payne. *Journal of Clinical Pathology* [*J. clin. Path.*] **14**, 309–312, May, 1961. 12 refs.

This paper from the Welsh National School of Medicine, Cardiff, records investigations into the use of bovine γ globulin and a British preparation of polystyrene latex particles in the latex fixation test for rheumatoid arthritis. Initial investigations demonstrated that spontaneous agglutination occurred in a standard latex suspension with bovine γ globulin in two ranges of concentration—$3{\cdot}1 \times 10^{-1}$ to $9{\cdot}8 \times 10^{-3}$ g. per 100 ml. and $3{\cdot}9 \times 10^{-4}$ to $4{\cdot}9 \times 10^{-5}$ g. per 100 ml. All concentrations from 2·5 g. per 100 ml. to *nil* were tested and, with the exception of these specified ranges, no agglutination occurred. In the presence of serum from patients with

rheumatoid arthritis agglutination failed to occur with concentrations of bovine γ globulin of $6{\cdot}3 \times 10^{-1}$ g. per 100 ml. and above. At concentrations between $6{\cdot}3 \times 10^{-3}$ and $7{\cdot}8 \times 10^{-4}$ g. per 100 ml. it was possible to obtain agglutination titres with a clear end-point. Prozoning did not occur as it did with concentrations of $4{\cdot}9 \times 10^{-5}$ g. per 100 ml. or below. A concentration of 5·0 mg. per 100 ml. was found to be the most satisfactory to give the highest titres with the majority of positive sera. Further experiments showed that the highest titres were evolved by bulk heating of the latex and γ globulin mixture and then adding it to the serum dilutions after cooling.

Duplicate tests were made on 300 specimens of serum using a standard latex test based on these principles and the sensitized sheep cell test as modified by Greenbury and Ball, with plastic agglutination trays. Assuming the result of the latex test to be positive with agglutination to a titre of 1:80 or greater, there was agreement in 264 of the 300 tests (88%). Some analysis is made of the cases giving divergent results, which, it is noted, included a number of cases of rheumatoid pneumoconiosis. The technique of the standard test evolved is set out in detail and shown to be inexpensive, easy, and quick to perform. The titres obtained by this latex technique showed no correlation with those of the sensitized sheep cell test. (In an addendum the results of a comparison of this latex test and the Hyland RA test, which utilizes human γ globulin as the reactant are reported. Agreement in 135 of 141 cases (95·7%) is recorded.

Harry Coke

982. **Rheumatoid Arthritis of the Crico-arytenoid Joint** A. GROSSMAN, J. R. MARTIN, and H. S. ROOT. *Laryngoscope* [*Laryngoscope* (*St. Louis*)] **71**, 530–544, May, 1961. 7 figs., 8 refs.

Laryngeal complications developing in the course of rheumatoid arthritis are rarely diagnosed during the patient's lifetime, though extensive changes may be demonstrable in the crico-arytenoid joint at necropsy. At the Montreal General Hospital 55 patients with rheumatoid arthritis were closely questioned and underwent examination of the larynx by the authors. Of these, 17 had some symptoms referable to the larynx. On mirror examination 18 patients showed some evidence of crico-arytenoid arthritis, but 9 of these had no laryngeal symptoms. In 5 out of 11 consecutive patients with rheumatoid arthritis who were examined post mortem there was evidence of rheumatoid involvement of the larynx, but only 2 of these patients had had any laryngeal symptoms during life.

The authors discuss the question why this condition is so often unrecognized. On examination of the larynx there may be redness and swelling of the mucosa over one or both crico-arytenoid joints, but in the authors' series this finding was noted only rarely. In some cases the joint becomes disorganized and ankylosed in a deformed position, while fixation of one or both true vocal cords may occur in the midline position. Fixation of one cord in the midline will not produce stridor or severe hoarseness and in a bedridden patient who has no need to exert himself this may even be true with bilateral fixation. Vocal change is not a common finding in these cases. Other symptoms that might be expected to be present, but are more often absent, are persistent sore throat, a feeling of "something sticking in the throat" after swallowing, and dysphagia. Even when symptoms and signs of laryngeal disease are present in a case of rheumatoid arthritis they may not necessarily be due to involvement of the crico-arytenoid joint. Darke *et al.* (*Brit. med. J.*, 1958, **1**, 1279; *Abstr. Wld Med.*, 1958, **24**, 441) reported that most of 5 cases of midline fixation of the cords clinically due to arthritis were proved at necropsy to be due to paralysis of the recurrent laryngeal nerve, while in one case the real cause was a laryngeal carcinoma. Other conditions to be excluded in differential diagnosis are the oedema of the area that may follow irradiation for carcinoma, laryngeal injury during endoscopy or endotracheal intubation for anaesthesia, prolonged feeding by nasal tube, and occasionally upper or lower respiratory-tract infection with suppuration of or around the joint

Stridor due to bilateral fixation of the vocal cords may necessitate surgical treatment in the form of tracheotomy or arytenoidectomy and cord lateralization Some patients with rheumatoid arthritis have such deformity of the fingers that they may find it difficult to attend to a tracheotomy orifice; for these in particular lateralization of the cord or arytenoidectomy is useful. The authors point out that in some cases arthritic change can make indirect examination of the larynx impossible. [In such an event endoscopy must be considered.] The histories of the 5 cases which came to necropsy are given in full and a further case is mentioned in which routine post-mortem examination of the crico-arytenoid joints in a patient who died of scleroderma revealed unsuspected non-suppurative arthritis. This suggests that such arthritis may occur in conditions other than rheumatoid arthritis.

[This is a valuable paper.] *F. W. Watkyn-Thomas*

983. **Cancer Arthritis and Rheumatoid Arthritis** B. STRANDBERG and N. V. JARLOV. *Archives of Physical Medicine and Rehabilitation* [*Arch. phys. Med.*] **42**, 273–278, April, 1961. 3 figs., 2 refs.

Reference is made to the similarity between the early symptoms of rheumatoid arthritis and those of many forms of cancer—that is, in the prodromal or early stages of both diseases and particularly before gross radiological changes can be detected in the rheumatoid joints. The authors then review their findings in 53 patients with rheumatoid arthritis admitted to the Copenhagen County Hospital during a recent 5-year period, a group of 91 healthy subjects serving for purposes of comparison.

The sex ratio (39 females and 14 males) conformed to that in rheumatoid arthritis. The patients could be divided into two groups: in the first the response to Hyland's rheumatoid arthritis test was positive in 26 out of 27 (96·3%) of the patients and in the second the response was positive in one out of 26 (3·8%). The response was positive in 5 (5·4%) of the 91 controls. The serum antistreptococcal hyaluronidase and streptolysin

titres and the results of the streptococcal agglutination test in the first group closely approximated those found in other series of cases of rheumatoid arthritis, while the values in the second group corresponded more closely to those obtained in the controls. The serum alkaline-phosphatase concentration was over 10 units in all except 2 patients in the second group. Paper electrophoresis showed that the serum protein fractions in the second group deviated significantly from normal and from those in the first group, particularly in respect of α_2-globulin content, which was raised in every case. Continued observation of the patients in the second group revealed that at the time the above findings were obtained all these patients were in the early stages of malignant disease at various sites, including cancer of the lung (5), uterus (5), and stomach (4).

The authors suggest that rheumatoid arthritis is not to be regarded as a disease *per se*, but as an arthritic manifestation of allergy to noxious products arising in various diseases of muscle and skin. They further suggest that the syndrome may be the first indication of malignant disease. *William Hughes*

COLLAGEN DISEASES

984. **Serum Transaminase Estimations in the Differential Diagnosis of Collagen Disease**
C. F. H. Vickers. *British Journal of Dermatology* [*Brit. J. Derm.*] **73**, 185–193, May, 1961. 2 figs., 29 refs.

The differential diagnosis of dermatomyositis from other collagen diseases, particularly from systemic lupus erythematosus, is sometimes difficult. The author, working at the Royal Infirmary, Sheffield, showed that the serum level of glutamic oxalacetic transaminase (G.O.T.) was raised in 5 out of 6 patients with dermatomyositis but in none of a series of 371 controls, including 14 patients with rheumatoid arthritis, 38 with discoid or systemic lupus erythematosus, and 19 with scleroderma and acrosclerosis. In 2 patients with dermatomyositis the serum G.O.T. level fell following administration of steroids. It is pointed out that the level is sometimes high in the absence of other laboratory evidence of muscle wasting.

The author concludes that estimation of the serum G.O.T. level is valuable in the diagnosis and assessment of activity of dermatomyositis. *G. L. Asherson*

985. **A Study of the Mechanism by which Quinacrine Inhibits L.E. Cell Formation**
N. Neilson and J. Lansbury. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **241**, 700–709, June, 1961. 2 figs., 13 refs.

Working at the Temple University School of Medicine, Philadelphia, the authors have studied the inhibition of L.E. cell formation in cases of systemic lupus erythematosus (L.E.) by quinacrine (mepacrine) in the hope that an understanding of this mechanism might shed light on the antirheumatic action of the drug.

Electrophoretic studies on serum incubated with quinacrine suggested no firm binding of the drug by protein, and ultraviolet-light studies of blood films after exposure to quinacrine showed a considerable concentration of the drug in leucocyte cytoplasm, with a little in the nuclei and none in the erythrocytes. The addition of quinacrine to suspensions of normal leucocytes in normal plasma almost abolished pseudopod formation and phagocytosis by leucocytes when the drug concentration was 0·4 mg. per ml. or more.

Prior treatment of potent L.E. serum with quinacrine followed by dilution to below 0·4 mg. per ml. did not interfere with L.E. cell production, suggesting that quinacrine does not inactivate the L.E. serum factor. Nor did exposure of a suspension of leucocyte nuclei to quinacrine prevent their conversion to L.E. bodies and subsequent phagocytosis when potent L.E. serum and leucocytes were added. This suggests that quinacrine does not inhibit the union of L.E. serum factor and nucleoprotein. Only when the concentration of quinacrine reached 0·4 mg. per ml. was L.E. cell formation inhibited and the authors believe this to be due to inhibition of phagocytosis. This drug concentration is far above therapeutic levels and the study does not help to explain the antirheumatic action of quinacrine.

M. Wilkinson

986. **A Clinical Study of Serum Antinuclear Factor**
D. M. Weir, E. J. Holborow, and G. D. Johnson. *British Medical Journal* [*Brit. med. J.*] **1**, 933–937, April 1, 1961. 39 refs.

This paper from the M.R.C. Rheumatism Research Unit, Canadian Red Cross Memorial Hospital, Taplow, describes the application of Coons's fluorescent antibody technique to the demonstration of an antinuclear factor (A.N.F.) in the serum of patients with systemic lupus erythematosus (S.L.E.) and certain other disorders. Sections of human infant thyroid tissue were incubated with test serum at 37° C. for 30 minutes and after careful washing were stained with a fluorescein *iso*cyanate or *iso*thiocyanate conjugate with anti-human-globulin serum. Under controlled conditions a nuclear fluorescence indicated a positive reaction for A.N.F. [It is stated that the positive nuclear fluorescence indicates an uptake of globulin from the test serum. Since some of the antisera used were directed against whole human serum, it is not clear which globulin component is being demonstrated.]

Positive A.N.F. reactions were obtained in 62 (98%) out of 63 cases of S.L.E., 19 (14%) of 132 of rheumatoid arthritis, 13 (13%) of 100 of Still's disease, and in 10 (13%) of 75 of discoid lupus erythematosus. Positive reactions were also obtained in 13% of 100 and 39 cases of thyroid and liver disease respectively. The reaction was negative in 56 cases of rheumatic fever and in 131 of 133 normal subjects. It is concluded that although in S.L.E. the A.N.F. reaction is persistently positive, a positive reaction is not in itself of diagnostic value.

The authors suggest that the A.N.F. in patients with S.L.E. may be the same as the factor responsible for the L.E.-cell phenomenon and they discuss the significance of the test from the diagnostic and aetiological points of view and in the light of Burnet's clonal theory.

Hewett A. Ellis

Neurology and Neurosurgery

987. **Restless Legs.** [In English]
B. BORNSTEIN. *Psychiatria et neurologia* [*Psychiat. et Neurol. (Basel)*] **141**, 165–201, March [received May], 1961. 2 figs., 22 refs.

The case histories of 22 patients with the " restless legs " syndrome are reported in this paper from Beilinson Hospital, Petah Tikua, Israel. The chief symptoms were paraesthesiae of the lower limbs on sitting still or lying in bed, rarely on standing, followed by restless movements which sometimes wakened the patient and were relieved by getting up and walking about. The upper limbs, neck, and abdominal wall were not often affected. There were no abnormal signs on examination and the results of special investigations, including electroencephalography, were negative. The disorder appears at any age, the youngest patient being 5 years and the oldest 82 years. There was often a hereditary and familial tendency. The condition first became manifest after brain injury or encephalitis and regressed after the development of diabetic peripheral neuropathy and lumbar radiculitis following disk protrusion. There was no effective treatment.

The cause is still unknown, but the author suggests that it may be related to the influence of a lesion of the reticular system on the gamma system. *I. Ansell*

988. **Blood Serum Levels in Intestinal Absorption of Vitamin B_{12} in Multiple Sclerosis**
V. GRANN and G. B. J. GLASS. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **57**, 562–567, April, 1961. 1 fig., 25 refs.

Investigation of the blood serum levels of vitamin B_{12} [cyanocobalamin] by the *Ochromonas malhamensis* method and study by the hepatic uptake method of the intestinal absorption of radioactive vitamin B_{12} in 21 cases of multiple sclerosis fail to indicate any significant vitamin B_{12} deficiency or B_{12} absorption defect in this disease.—[Authors' conclusions.]

989. **Intermittent Claudication of the Cauda Equina. An Unusual Syndrome Resulting from Central Protrusion of a Lumbar Intervertebral Disc**
J. N. BLAU and V. LOGUE. *Lancet* [*Lancet*] **1**, 1081–1086, May 20, 1961. 5 figs., 14 refs.

The authors describe 6 cases, observed among 300 consecutive cases of lumbar-disk protrusion, in which the presenting symptoms were intermittent pain and paraesthesiae in the distribution of the lower lumbar or sacral dermatomes on walking a certain distance. The sensations were described typically as pins-and-needles, usually painful and burning, starting in the feet and extending up the calf into the lower thighs. The character of the paraesthesiae, the site of pain, and the definite march of sensations from area to area are features which differentiate the condition from claudication due to aortic obstruction. The pain was relieved completely after 30 seconds to 3 minutes by standing still or sitting down.

All these patients had some neurological signs of cauda equina involvement, but these varied from very slight to a nearly complete picture. Although there were usually some plain x-ray changes and a raised cerebrospinal-fluid protein level, diagnosis finally depended on myelography, which showed a block at the intervertebral disk. Five out of the 6 cases were operated on and all patients were entirely relieved of intermittent dysaesthesiae and pain and all returned to work.

The authors, discussing the mechanism, postulate that walking demands an increased blood flow to the cauda equina roots, and that this is prevented by the disk pressure with the result that a relative ischaemic neuritis develops. *N. S. Alcock*

990. **Carpal Tunnel Syndrome: Treatment by Splinting**
C. E. QUIN. *Annals of Physical Medicine* [*Ann. phys. Med.*] **6**, 72–75, May, 1961. 4 refs.

In 1957, Heathfield (*Lancet*, **2**, 663; *Abstr. Wld Med.*, 1958, **23**, 128) reported that splinting of the wrist in the neutral position was successful in the treatment of acroparaesthesiae due to compression of the median nerve in the carpal tunnel in 48 of 51 cases. The present author has reviewed his findings at the Royal Sussex County Hospital, Brighton, in 47 cases of carpal tunnel syndrome and notes that with this mode of treatment improvement occurred in 28 patients. Of the 19 patients who did not improve with splinting, 11 were given an injection of 25 mg. of hydrocortisone acetate into the carpal tunnel and this procedure was successful in relieving symptoms in 8 cases.

[In this clinical trial patients were kept under observation for periods ranging from 2 months to over a year. It is evident that there must have been a number of early relapses in the 28 cases of carpal tunnel syndrome which are reported as having responded to conservative treatment with splinting, as the author states that subsequently " some received hydrocortisone injections into the carpal tunnel or were referred for operation ".] *A. G. Freeman*

991. **Methacholine and Noradrenaline Tests: their Reliability and Physiological Significance**
E. GELLHORN and A. D. MILLER. *Archives of General Psychiatry* [*Arch. gen. Psychiat.*] **4**, 371–380, April, 1961. 2 figs., 32 refs.

The authors set out to determine the validity of intramuscular injections of methacholine and noradrenaline as tests to measure autonomic reactivity. The tests with methacholine were carried out 3 times in one week on 44 normotensive patients and those with noradrenaline a similar number of times on 47 normotensive patients,

The results were evaluated on the basis of 5 parameters for noradrenaline and 5 for methacholine which indicated the sympathetic reactivity in the response to methacholine and the parasympathetic reactivity in response to noradrenaline. The reliability of the tests was found to be statistically significant. The patients can be grouped in each test into three groups with decreasing parasympathetic or sympathetic responsiveness. The tests are recommended for use in clinical studies to determine whether changes in sympathetic or parasympathetic reactivity occur as the result of treatment, and which changes, if any, are significantly related to clinical improvement. *J. B. Stanton*

DIAGNOSTIC METHODS

992. **Ultrasonics in the Diagnosis of Intracranial Space-occupying Lesions**

J. C. TAYLOR, J. A. NEWELL, and P. KARVOUNIS. *Lancet* [*Lancet*] **1**, 1197–1199, June 3, 1961. 1 fig., 13 refs.

To apply the echo-sounding principle to the location of intracranial structures the authors use an ultrasonic instrument designed and built at the Royal Marsden Hospital, London, which combines a working frequency as high as 2·5 megacycles per second with a sensitivity adequate to detect the resulting echoes, which are displayed as vertical pulses on a horizontal 15-mm. scale marked on a cathode-ray tube. Various echoes are obtained from interfaces within the skull, but the most constant and largest are from the midline structures and displacement of them, indicating the presence of a space-occupying lesion, can rapidly be calculated from any difference in the measurements of the distance between surface and midline as between symmetrically situated portals. Glucose syrup is used as the "coupling" medium between the crystal probe and the patient's scalp and it is not necessary to shave the head. An apparent displacement of more than 3 mm. is considered significant.

At Atkinson Morley's Hospital (St. George's Hospital), London, 280 patients were examined by this method, 248 undergoing further investigations such as carotid angiography or ventriculography. In 32 cases the ultrasonic prediction of absence of a space-occupying lesion was not verified. Of the remainder, accurate prediction of a space-occupying lesion was made in 86 cases and accurate exclusion in 130. In 17 cases the ultrasonic method failed to predict the tumour which was present and in one case a tumour was falsely predicted which was not present. In 12 cases (4%) the method did not give good echoes.

The authors comment that an accuracy of 90% with a safe, painless, and quick method of investigation represents a real contribution to neurological diagnosis—even though it detects only the displacement of midline structures. It has been especially useful in differentiating space-occupying haematomata from cerebrovascular accidents.

[This would appear to be an interesting development and one which merits further study.] *N. S. Alcock*

993. **The Electroencephalogram in Cases of Benign Intracranial Hypertension**

A. D. SIDELL and D. D. DALY. *Neurology* [*Neurology (Minneap.)*] **11**, 413–417, May, 1961. 2 figs., 9 refs.

At the Mayo Clinic the authors examined the electroencephalograms (EEGs) of 16 patients suffering from benign intracranial hypertension. Eleven were within normal limits. In 5 cases 4- to 7-c.p.s. activity was present, but 3 of the 5 were doubtfully abnormal in that 2 showed only infrequent theta activity and one was from a child of 9 years. Of the 2 patients with unequivocally abnormal records, one was a boy of 16 whose EEG showed occasional bursts of theta activity in the temporal electrodes and who had had a head injury in the past which might have been responsible for these abnormalities. The second patient, a woman of 31, had brief recurrent bursts of diffuse theta activity in her EEG, the duration of which was increased by hyperventilation.

These findings contrast with those in a previously reported group of patients with hydrocephalus (Daly *et al.*, *Electroenceph. clin. Neurophysiol.*, 1953, **5**, 203), 84% of whom had abnormal records, and support the conclusions of Stewart (*Bull. Johns Hopk. Hosp.*, 1941, **69**, 240) that a generalized increase in intracranial pressure does not produce electroencephalographic abnormalities. *H. S. Schutta*

BRAIN AND MENINGES

994. **Cortical and Subcortical Disturbances of Function following Cardiac Arrest in Relation to the Neuropathological Findings.** (Über die corticalen und subcorticalen Funktionsstörungen infolge von Herzstillstand. Vergleich zum neuro-pathologischen Befund)

J. SAYK. *Archiv für Psychiatrie und Nervenkrankheiten* [*Arch. Psychiat. Nervenkr.*] **201**, 565–579, 1961. 5 figs., bibliography.

Two cases of cardiac arrest after lung operations are reported. A man of 33 survived 3 months after cardiac arrest lasting 3½ minutes. He could chew and swallow, but had a flaccid tetraplegia. For most of the time the patient was unconscious, but partial consciousness returned for short periods, presenting a picture similar to that of schizophrenic stupor. At necropsy the brain showed a severe status spongiosus with gross loss of nerve cells in the frontal, parietal, and occipital cortex and necrosis of the pallidum. The other basal ganglia showed moderate lesions. The cerebellar cortex showed considerable loss of Purkinje cells. The supra-optic, vagus, and hypoglossal nuclei were completely intact. A woman of 31 with a history of 6 minutes' cardiac arrest, seizures, and 3 weeks' unconsciousness finally learned to speak, read, and walk again. As the cortical functions recovered the subcortical disturbance (Parkinsonism) resulting from lesions of the basal ganglia became apparent. The level of cerebral function reached the mental age of about 8 to 9 years, when there was no further progress and she was left with a slight defect.—[From the author's summary.]

995. **Wernicke's Encephalopathy: a Clinical and Pathological Study of 28 Autopsied Cases**
H. CRAVIOTO, J. KOREIN, and J. SILBERMAN. *Archives of Neurology* [*Arch. Neurol. (Chicago)*] **4**, 510–519, May, 1961. 8 figs., 32 refs.

This paper from the New York University Medical Center reviews 28 cases in which the characteristic histopathological changes of Wernicke's encephalopathy were found at the post-mortem examination. The variations and distribution of the pathological lesions and the clinical features of these cases are discussed. Besides the typical vascular lesions in the mammillary bodies and the relative preservation of neurones, varying degrees of "astrocytosis" were noted which could not be correlated with the degree of tissue destruction. This finding was most prominent in the thalamus. The possibility of a primary defect in the astrocytes related to altered thiamine metabolism is discussed.

The clinical findings suggest that the diagnosis of Wernicke's encephalopathy should be considered in chronic alcoholics with an organic mental syndrome, hypotension, and lethargy despite the absence of the so-called characteristic clinical picture, which was present in only 4 of the 28 cases in the present series.

J. MacD. Holmes

996. **Analysis of Occlusive Disease of the Carotid Artery and the Stroke Syndrome**
E. S. GUARDJIAN, W. G. HARDY, D. W. LINDNER, and L. M. THOMAS. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **176**, 194–204, April 22, 1961. 9 figs., 17 refs.

Arteriography in the diagnosis and the surgical management of cerbrovascular disease are discussed on the basis of experience in 720 patients seen at Wayne State University College of Medicine and the Grace and Detroit Memorial Hospitals, Detroit, between 1956 and 1960. Stenotic lesions of the carotid bifurcation and the internal carotid artery were present in 157 patients. In 34 with carotid stenosis surgical treatment consisted in endarterectomy (26), removal of thrombus (5), and ligation, grafting, and external–internal carotid anastomosis (one each). The surgically treated group represented 21% of patients with carotid stenosis and 5% of all patients with cerebrovascular disease. The indications for withholding operation from patients with proved carotid stenosis were associated occlusive disease higher in the neck or in the cranial cavity or both on the same side (71 patients) and occlusion of the carotid artery on the opposite side (11). The remaining patients had associated subarachnoid haemorrhage, intracerebral or subdural haematoma, brain tumour, Parkinson's disease, syphilis, or small bilateral lesions at the bifurcations.

The authors consider that the prognosis in patients with stenosis of the carotid artery in the neck depends on: (1) the collateral circulation, (2) embolization from atheromatous ulcers, and (3) concomitant occlusive involvement of the vessel or its branches higher up. They discuss the indications for operation, the possible value of endarterectomy, ligation, and cervical sympathectomy, and the role of mechanical extravascular factors in the aetiology of cerebrovascular insufficiency.

[This interesting paper was read at a conference and detailed publication is promised. It is hoped that this will clear up some ambiguities and give follow-up evidence on which surgical treatment of carotid stenosis can be evaluated.] *Bernard Isaacs*

997. **Carotid Occlusion: Its Diagnosis by Ophthalmodynamometry during Carotid Compression**
R. D. LOWE and N. L. STEPHENS. *Lancet* [*Lancet*] **1**, 1241–1245, June 10, 1961. 5 figs., 20 refs.

In only 6 out of 28 cases of carotid occlusion in man was there a significant difference between the retinal artery pressures in the two eyes. Investigations in rabbits suggested a modified test for the presence of carotid occlusion in man, using ophthalmodynamometry with carotid compression. Twenty-five out of 28 cases (93%) of carotid occlusion were clearly distinguishable from normal by this test.—[Authors' summary.]

998. **Studies in Headache: Electroencephalographic Abnormalities in Patients with Vascular Headache of the Migraine Type**
W. A. CAMP and H. G. WOLFF. *Archives of Neurology* [*Arch. Neurol. (Chicago)*] **4**, 475–485, May, 1961. 5 figs., 24 refs.

Reports in the literature show that when a large number of patients complaining of headache are studied by means of electroencephalography the distribution of normal and abnormal records is approximately the same as in a headache-free population. Among patients with vascular headaches of the migraine type, however, the incidence of abnormal electroencephalograms (EEGs) increases to about double that found in healthy subjects. The authors of this paper from the New York Hospital point out that the abnormal EEGs in such cases fall into two broad categories. (1) In this category are the EEGs taken during the headache-free period that show a persistent non-focal abnormality. These records show predictably paroxysmally or diffusely occurring 4- to 7-c.p.s. activity in excessive amounts. The genesis of these disturbances is not known, but a relationship to epilepsy has been suggested. (2) In this category are EEGs showing focal abnormalities. There are three groups: (*a*) EEGs that are altered very briefly during an attack of vascular headache of the migraine type with fleeting motor or sensory disturbances (short-lived ischaemia due to vasoconstriction probably being the initiating event); (*b*) EEG abnormalities that develop during an attack of vascular headache associated with defects of motor, sensory, or mental function and disappear within hours or days, concurrently with resolution of the clinical signs (local oedema of the brain being a likely cause); and (*c*) EEGs taken during the headache-free period that show a persistent focal abnormality occurring most frequently in patients with marked motor, sensory, or mental abnormalities during one or other phase of the migraine attack (cerebral infarction being suggested as the precipitating accident).

J. MacD. Holmes

999. **Transitory and Repeated Cerebral Arterial Accidents of Simulated Spastic Origin. Effective Surgical Treatment.** (Accidents artériels cérébraux passagers et répétés, simulant une origine spasmodique. Traitement chirurgical efficace)
C. LIAN. *Presse médical* [*Presse méd.*] **69**, 761–764, April 8, 1961.

The author points out that many cerebrovascular incidents are unaccompanied by thrombosis and depend on a fall in the central blood pressure and narrowing by atherosclerosis of the cerebral arteries; he cites evidence against spasm of these arteries playing any part. On the other hand he has been so impressed by the excellence of the response of his patients to the Sousa Pereira procedure that he is unwilling to admit the complete absence of a beneficial vasodilatation after cervical sympathectomy. The Sousa Pereira procedure, carried out unilaterally under local anaesthesia, consists in tying the external carotid artery, performing a periarterial sympathectomy of the internal carotid artery, and resecting the superior cervical sympathetic ganglion. He quotes Sousa Pereira as having found by cerebral arteriography in man (and also experimentally in dogs after cerebral arterial ligation) that the cerebral circulation is improved on the side of the sympathectomy.

The author then quotes the case histories of several patients in whom recurrent transient cerebral ischaemic attacks had been abolished or much alleviated for long periods by the Sousa Pereira operation. He suggests that in patients suffering repeated incidents lasting only a few minutes at a time this very benign procedure is likely to succeed. Success is less likely in the case of protracted attacks, though it may be attained when the attacks are separated by an interval of several months or a year. After a single grave incident there is often considerable spontaneous improvement and it is difficult to assess the value of the procedure. Sousa Pereira advises a preliminary procaine block of the cervical sympathetic ganglion, with recourse to the operation if this procedure results in clear improvement. The use of ephedrine to guard against a fall of central blood pressure is regarded as a useful adjunct. *C. J. Longland*

1000. **Morphological Studies on the Large Cerebral Arteries: with Reference to the Aetiology of Subarachnoid Haemorrhage.** [Monograph, in English]
O. HASSLER. *Acta psychiatrica et neurologica Scandinavica* [*Acta psychiat. scand.*] **36**, Suppl. 154, 1–145, 1961. 35 figs., bibliography.

1001. **The Diagnostic Value of Psychiatric Abnormalities in Cases of Tumour of the Temporal Lobe.** (Über den diagnostischen Wert psychiatrischer Befunde bei temporalen Hirntumoren)
H. OEPEN. *Archiv für Psychiatrie und Nervenkrankheiten* [*Arch. Psychiat. Nervenkr.*] **201**, 465–482, 1961. 6 figs., 9 refs.

The author has studied the relationship between the different psychiatric symptoms and the nature and site of the pathological process in 80 patients with space-occupying lesions in the temporal lobes. [The series is too small to allow definite conclusions to be reached, but a few interesting trends have emerged from the study.] The type of tumour and presence or absence of papilloedema bear no recognizable relationship to the occurrence of paroxysmal or non-paroxysmal localizing psychic symptoms. While 34 patients had seizures, 8 of these were psychomotor attacks and only 3 had uncinate fits. Aphasia is usually associated with left-sided lesions of the speech centres, whereas right-sided lesions or left-sided lesions in the vicinity of the speech centres tend to produce pressure of speech. Disturbances of motor drive are often associated with right-sided lesions (particularly in women) and are more common if the lesion is in the base of the temporal lobe. Affective anomalies are associated with right-sided lesions in women and left-sided lesions in men. *J. Hoenig*

1002. **False Localizing Signs: a Review of the Concept and Analysis of the Occurrence in 250 Cases of Intracranial Meningioma**
M. M. GASSEL. *Archives of Neurology* [*Arch. Neurol. (Chicago)*] **4**, 526–554, May, 1961. Bibliography.

The records of 250 consecutive confirmed cases of intracranial meningioma admitted to the National Hospital, Queen Square, London, in the period 1948–58 have been studied with reference to false localizing signs. The study incorporates the presenting and preoperative findings, and on this basis 101 cases were found to have some false localizing signs.

There were no visual field defects in the preoperative course of illness which obscured the diagnosis or could be classed as false localizing signs. The absence of bitemporal or binasal field defects as false localizing signs in this study is probably related to the fact that in 230 of the 250 cases the meningioma was supratentorial. Signs of false localizing chiasmal compression are said to occur when internal hydrocephalus is pronounced, with marked distension of the third ventricle and especially in tumours of the posterior fossa. Infarction of the occipital lobe distant to an intracranial tumour is an established but infrequent post-mortem finding; it generally occurs in the agonal period and is without clinical analogy. Visual field defects were found to be an invariably valid and highly effective clinical means of location of tumours in the present study.

The third nerve was affected in 40 instances. Pupillary inequality as the only evidence of third-nerve involvement was present in 15 cases; in 12 of these the pupil ipsilateral to the tumour was smaller. When anisocoria was combined with other evidence of third-nerve disorder the ipsilateral nerve was affected in 8 cases and the contralateral nerve in 2 cases. All these patients had larger pupils on the side of the involved nerve, except for one patient with ipsilateral third-nerve signs. Ptosis was present in 18 cases—13 ipsilateral to the tumour, 3 contralateral, and 2 bilateral. Other third-nerve extraocular muscle pareses occurred in 5 cases.

Paralysis of the fourth nerve did not occur as a false sign in this series, its absence being related to the extensive, tortuous extramedullary course of this nerve.

Involvement of the fifth cranial nerve occurred in 8 cases—5 ipsilateral to the tumour and 3 contralateral.

The motor part was affected in 2 cases, and in one of these was the only evidence of fifth-nerve palsy. Sensory impairment was manifested in 2 cases by a depressed corneal reflex and in the other cases by hypaesthesia in the first division in one, the first and second divisions in 2, and in all 3 divisions in 2 others. The impaired sensation to pinprick was more pronounced than to cotton-wool in 2 cases. There were 14 cases with lateral rectus palsy—5 bilateral, 3 ipsilateral, and 6 contralateral. This sign is frequent with increased intracranial pressure from any cause.

Nystagmus was noted in 6 patients with supratentorial meningioma, excluding patients receiving barbiturates and those with nystagmus in association with false localizing cerebellar signs. The nystagmus was generally of jerky type and occurred only on lateral horizontal deviation, never on elevation or depression, of the eyes. It was bilateral in 2 cases, noted on ipsilateral deviation in 3 cases, and on contralateral horizontal deviation in one case.

There were 6 examples of proptosis as a false localizing sign. It was recorded as such only when the meningioma was located at a distance from the posterior orbit and sellar region. The proptosis was usually of slight degree. In 2 cases it was ipsilateral to the tumour, in one contralateral, and in 3 bilateral, and was found only in the presence of raised intracranial pressure.

S. J. H. Miller

1003. **Primary Reading Epilepsy**

D. W. Baxter and A. A. Bailey. *Neurology* [*Neurology* (*Minneap.*)] **11**, 445–449, May, 1961. 3 figs., 9 refs.

From the University of Saskatchewan College of Medicine the authors report 2 cases in which myoclonic jerks of the jaw were brought on by reading and in one case were accompanied by generalized seizures.

In the first case, that of a male aged 19 years, jerking movements of the jaw occurred after reading aloud for 10 minutes or after longer periods of silent reading. The resting electroencephalogram (EEG) was stable. After 5 minutes' silent reading low-voltage sharp waves occurred in the temporal areas and after 9 minutes moderate-voltage spikes and spikes and slow waves appeared, maximal in the right temporal area, associated with low-amplitude jaw opening movements on one occasion. Reading aloud for one minute evoked jerking of the jaw and high-voltage multiphasic spikes which were, however, thought to be muscle artefacts. The symptoms subsided spontaneously. The second patient, a boy of 15, reported that one day while he was reading silently alone his jaw opened involuntarily, his limbs stiffened, and he became unconscious for an unknown period, after which he felt dizzy and found that he had bitten his tongue. Four weeks later he had a similar episode when it was observed that his body went stiff and became arched and he made repetitive noises, though no clonic movements were seen. He was unconscious for several minutes and confused for a further 15 minutes. The EEG showed short bursts of theta activity on hyperventilation. During 15 minutes' reading the EEG activity consisted mainly of moderate-voltage 5- to 7-c.p.s. activity; this record, however, was considered to be within normal limits. Neither of the patients had seizures under any other circumstances and the family history was negative in both cases.

It is suggested that repeated proprioceptive stimuli from the eye and facial musculature and repeated visual stimuli may provoke abnormal activity in the reticular formation and trigeminal motor nuclei, giving rise to myoclonic jerks and seizures in susceptible persons.

H. S. Schutta

1004. **Electroencephalographic Abnormalities in Epileptics Who Fall on their Head during an Attack Compared with those Who do Not.** (EEG-Befunde bei Epileptikern, die im Anfall auf den Kopf stürzen, im Vergleich zu denen bei anderen Anfallskranken)

I.v. Hedenström and G. Schorsch. *Archiv für Psychiatrie und Nervenkrankheiten* [*Arch. Psychiat. Nervenkr.*] **201**, 502–507, 1961. 10 refs.

At the Bethel Institution, Bielefeld, the electroencephalograms (EEGs) of 75 epileptics who fell on their head during seizures (Group A) were compared with those of an equal-sized control group of epileptics who did not fall on their head (Group B). In both groups recordings were taken between fits and also immediately after a fit. In Group A there were more paroxysmal EEG abnormalities than in Group B and the general abnormalities were more pronounced, but these differences could be explained by differences in frequency and type of seizure. The amount of focal EEG abnormality was equal in the two groups, but in spite of that Group A showed a worse prognosis as regards psychic complications than the control group. More than twice as many patients in Group A than in Group B required to be placed in wards with extra nursing care. In 78·7% of all 150 cases the EEG was more disturbed after a seizure than in the interval. In the other 21·3% there was no difference.

J. Hoenig

1005. **Chlorphenoxamine Hydrochloride in Parkinsonism: a Controlled Trial**

P. R. Uldall, J. N. Walton, and D. J. Newell. *British Medical Journal* [*Brit. med. J.*] **1**, 1649–1652, June 10, 1961. 2 refs.

The authors report, from the Royal Victoria Infirmary, Newcastle upon Tyne, a controlled clinical study by the double-blind method of chlorphenoxamine hydrochloride, a drug closely related chemically to diphenhydramine hydrochloride (" benadryl "), in 17 cases of Parkinsonism. Each patient was given the trial drug for 3 months and dummy tablets for a similar period. The effect of the treatment was estimated subjectively and objectively, the latter by observation of tremor, rigidity, and the ability to open and close the hands rapidly.

The results were equivocal. Seven of the 17 cases improved more with the drug than with the control tablets, 6 more with the placebo than the drug, and 4 could not differentiate between the two treatments. Objective clinical assessment of the drug revealed no effect on tremor or rigidity, but a significant improvement in the ability to open and close the hands rapidly.

R. Wyburn-Mason

Psychiatry

1006. **The Effect of Drugs on the Conditional Psychogalvanic Reflex in Man**
L. ALEXANDER and S. R. HORNER. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] **2**, 246–261, June, 1961. 13 figs., 21 refs.

This paper from Tufts University Medical School and Boston State Hospital describes a study of the effects of a number of drugs on the conditioned psychogalvanic reflex. This was established by pairing a tone with an electric stimulus to the index finger, while another tone, presented in regular alternation with this reinforced tone at one-minute intervals, was never so reinforced. The fall in skin resistance in response to the reinforced and unreinforced (inhibition) tones was measured. The subjects were 70 patients with various mental illnesses and 7 normal control subjects. All were tested before and after administration of one or more drugs, which included meprobamate, benactyzine, chlorpromazine, iproniazid, and nialamid. Nine patients were also tested before and after electric convulsion therapy (E.C.T.).

E.C.T. brought about a consistent significant increase in the positive conditioned psychogalvanic reflex with a trend toward improved differentiation in patients with an inhibitory pre-treatment response pattern, whereas the monoamine oxidase inhibitors and phenothiazines produced a marked and consistent decrease in all responses without significantly altering the differentiation between excitatory and inhibitory signals.

The significance of these and other findings are discussed and suggestions made for further research.

B. M. Davies

1007. **Experimental Analysis of Hysterical Blindness: Operant Conditioning Techniques**
J. P. BRADY and D. L. LIND. *Archives of General Psychiatry* [*Arch. gen. Psychiat.*] **4**, 331–339, April, 1961. 2 figs., 7 refs.

An experimental analysis of hysterical blindness of 2 years' duration by use of " operant " conditioning techniques is reported in this paper from Indiana University Medical Center, Indianapolis. The patient was required to press a button in a prescribed fashion so as to space his responses at intervals of 18 to 21 seconds. Responses falling within this range counted as the patient's " score " and were reinforced at first by auditory signal (buzzer) and later by visual stimuli of different types. Intervals between responses were automatically timed by electronic equipment, which also reset the apparatus after each response. It was found that anxiety, which was associated with the initial introduction of visual cues, tended to produce a number of early (faulty) responses, and with continued testing it became clear that the patient's score was improving by the use of visual cues. This was pointed out to the patient and resulted in recrudescence of anxiety, but eventually the patient admitted that he could see to some extent. He is now employed and has had no relapse in the 13 months since he first reported that he could see.

The case is presented primarily to illustrate the application of operant conditioning techniques to the study of psychiatric disorders.

J. B. Stanton

1008. **The Systematic Desensitization Treatment of Neuroses**
J. WOLPE. *Journal of Nervous and Mental Disease* [*J. nerv. ment. Dis.*] **132**, 189–203, March [received May], 1961. 29 refs.

The author, who writes from the University of Virginia School of Medicine, Charlottesville, holds the view that neurotic illness consists of habits of maladaptive behaviour acquired by learning and remediable by unlearning. If anxiety, the core of neurotic behaviour, can be reduced in the presence of the anxiety stimuli, the strength of the neurotic response habit will be gradually weakened. A widely applicable method of inhibiting anxiety is deep muscle relaxation, and the technique of systematic desensitization involves 3 steps: (1) training in relaxation; (2) construction of anxiety " hierarchies "; and (3) counterposing relaxation and anxiety-evoking stimuli from the hierarchies.

Before proceeding a detailed history is taken, with emphasis on all anxiety-producing circumstances. After classifying the sources of anxiety into thematic groups the patient ranks the items of each group from most to least disturbing. Concurrently, relaxation training is started; the patient is systematically made aware of tension (by contraction), then of deliberate relaxation, of all voluntary muscle groups. The desensitization procedure consists in presenting first " weak ", then progressively " strong " anxiety-arousing situations to the deeply relaxed patient, the 45-minute sessions usually being conducted under hypnosis. Starting with a neutral scene, the patient is asked to imagine for 5 to 15 seconds that he is in situations presented from the hierarchies; if he signals that it is disturbing it is terminated earlier. Each presentation is followed by deliberate relaxation. If no anxiety is elicited by several presentations of a scene the next one in the hierarchy is introduced. The number of sessions required for desensitization varies; in the case material here reported it ranged from 6 to 217, with a median of 10.

Details are given of 39 patients selected at random from 150 treated by this method. Desensitization was judged effective in 35 of the 39 patients. Of these 35, 20 were followed up for 6 months to 4 years after treatment; in no case was a relapse or the appearance of other neurotic symptoms reported. Some sceptical and critical views of this method of treatment are discussed.

Alan A. Black

MENTAL DEFICIENCY

1009. **Electroencephalographic Findings in Mentally Defective Children.** (EEG-Befunde bei abnormen Kindern)
K. RICHTER and D. JACHNIK. *Archiv für Psychiatrie und Nervenkrankheiten* [*Arch. Psychiat. Nervenkr.*] **201**, 605–625, 1961. 31 refs.

The electroencephalographic (EEG) findings in 393 patients from a child psychiatric clinic are evaluated. In particular the problem of the EEG differentiation between "endogenous" and "exogenous" subnormality was re-examined. The group of "endogenous" borderline defectives and the group of non-brain-damaged children with behaviour disorders showed the same percentage of borderline (11%) and definitely pathological (7 to 8%) EEGs. The "endogenous" subnormal and severely subnormal group showed a distinctly higher incidence of abnormal EEGs, namely, 8% borderline and 31% pathological. The "exogenous" mildly defective group showed 18% borderline and 24% pathological EEGs. The "exogenous" subnormal and severely subnormal group showed 4% borderline and 24% pathological records. The similar distribution of abnormal EEGs in the mild "endogenous" and "exogenous" groups as opposed to the differences in the subnormal and severely subnormal "endogenous" and "exogenous" groups raises the question whether the supposedly endogenous group of that severity does not contain a hidden exogenous group of unknown aetiology. Apart from these differences there were no correlations between the EEG and the severity of defect or the findings on air encephalography. The exogenous group gave a more frequent history of epileptiform seizures.

J. Hoenig

1010. **Mongolism Related to Emotional Shock in Early Pregnancy.** [In English]
D. H. STOTT. *Vita humana* [*Vita hum. (Basel)*] **4**, 57–76, 1961. 2 figs., 29 refs.

At the University of Glasgow the relationship between emotional shock in early pregnancy and mongolism was studied in the replies to a comprehensive questionary sent to the parents of 739 mongol children and 400 non-mongol retarded children. The questions related particularly to shock or injury to the mother during pregnancy and the type of such shock.

The incidence of emotional shock during the second and third months of pregnancy leading to a mongol birth was nearly twice as high as in any other month. The preponderance of shock during the first trimester was highly significant when compared with the incidence for the non-mongol births and with the theoretically even chance of shock at any time. In pregnancies leading to non-mongol defective children the incidence of emotional shock was highest during the second trimester. The incidence of physical injury was highest during the second trimester both for mongols and non-mongols.

The tendency to increased incidence of noxious agents during the later non-critical months—observed also in studies of rubella and influenza—and the possibility of a miscalculation of the date of conception are discussed. The concentration of psychogenic shocks during the second and third months of pregnancies leading to mongol births was noticed particularly when the shocks were "lasting" rather than when they were "ephemeral". Suggestions are made for correlating these findings with recent work on chromosome anomalies in mongols and other defectives.

E. H. Johnson

ORGANIC DISORDERS

1011. **The Influence of Complicating Physical Diseases on the Clinical Picture and Course of Cerebral Arteriosclerosis.** (Über den Einfluss komplizierter körperlicher Erkrankungen auf das klinische Bild und den Verlauf zerebraler Arteriosklerosen)
R. DEGKWITZ. *Fortschritte der Neurologie, Psychiatrie und ihrer Grenzgebiete* [*Fortsch. Neurol. Psychiat.*] **29**, 268–295, May, 1961. Bibliography.

At the Neurological Clinic of the University of Frankfurt am Main the author investigated 484 patients admitted with signs of cerebral arteriosclerosis. In 122 cases (25%) the course was simple and uncomplicated and these patients were excluded from further investigations. In the remaining 362 cases cerebral vascular obstruction or haemorrhage occurred 207 times and other complicating physical diseases 263 times (both occurring in many cases). Of these 362 patients with complications, 328 (90·6%) were admitted with acute psychotic disturbances. These fell into three groups: (1) those with definite focal symptoms such as aphasia (85 patients); (2) those with an acute exogenous reaction as described by Bonhoeffer, characterized clinically by delirium with restlessness, anxiety with paranoid ideas, hallucinations, amentia, incoherence of thinking, and affective lability (218 patients); and (3) those suffering from amnestic syndromes with impaired grasp and judgment, frequently associated with depression and/or hostile attitudes towards the environment, usually leading to failure of adaptation when faced with changes of situation (25 patients). (Case histories illustrative of Groups 2 and 3 are given.) The physical illnesses leading to symptomatic psychoses in 263 cases were: cardiac decompensation (121), infection (91), fractures (16), intoxication (13), carcinoma (11), and diabetes mellitus (11). Cardiac decompensation and infection thus provided the immediate precipitating cause in 91·3% of cases. Of these patients, 43% died, 27% recovered without residual effects, and 30% recovered with marked residual disability.

The high frequency of symptomatic psychoses in cerebral arteriosclerosis led the author to attempt to assess the cerebral blood volume and oxygen consumption (by Bernsmeier's modification of Kety's nitrous oxide method), but technical difficulties with the psychotic patients and problems of interpretation made this investigation useless. Estimation of the "active" blood volume of the body by the azovan blue method generally gave a diminished value. This returned to normal when the psychosis subsided. In 30 cases estimations of the oxygen saturation of the cerebral venous blood with the

Van Slyke apparatus were made; readings between 36·31 and 66·20% were obtained, corresponding to oxygen pressures of between 28 and 19 mm., which represents definite hypoxia. As further evidence of decreased total body fluid the author found that in symptomatic psychoses following cardiac decompensation no oedema was present and there were always signs of general dehydration. If—against all medical therapeutic rules—these patients were given extra fluid (2,000 to 2,500 ml.) by mouth the psychosis subsided within 24 hours. Signs of dehydration were also found in symptomatic psychoses following infections. After a rapid intravenous infusion of 500 to 1,000 ml. of Ringer's solution given over 10 to 20 minutes the psychosis was interrupted for 10 to 20 hours or subsided altogether. Immediately after the infusion most of the Ringer's solution had disappeared from the circulation. Using the sodium thiocyanate method of Crandell *et al.* the author found an increase of the extracellular fluid in several cases.

The author regards his findings as evidence that diminished circulatory volume and oxygen deficiency participate in the causation of symptomatic psychoses in cerebral arteriosclerosis. But this applies also, to a certain degree, to symptomatic psychoses arising without cerebral arteriosclerosis, for example, those occurring in infections and during the puerperium. Without giving details the author states that in these cases too infusions of 1,000 ml. of Ringer's solution can bring about rapid improvement, whereas in symptomatic psychoses in connexion with concussion or alcoholic or barbiturate poisoning no such results are achieved.

H. H. Grosser

AFFECTIVE DISORDERS

1012. **Atypical and Little-known Forms of Depression.** (Formes atypiques et méconnues de la mélancolie)
M. Riser, J. Laboucarié, A. Peyrevidal-Lacassin, and P. Lacassin. *Annales médico-psychologiques* [*Ann. méd.-psychol.*] **119**, 417–446, March [received May], 1961. 42 refs.

Apart from the well recognized depressive syndromes, including unusual forms associated with confusion and stupor, other and less familiar types occur which resemble schizophrenic states, systematized delusional states, and states of dementia. In a clinical study from the Neuropsychiatric Clinic of the University of Toulouse the authors postulate certain criteria for these atypical depressions: a favourable response to electric convulsion therapy (E.C.T.), a periodic course without deterioration, and ultimately a frankly depressive state. They review the history of melancholia from the time of Hippocrates to that of Kräpelin, extensively quoting from more modern authors to support the contention that the age of the patient has an important influence upon the clinical features. Atypical depression may resemble a schizophrenic illness in youth, a paranoid state in adult life, and dementia in old age.

The schizophreniform type is often reactive to stress, is periodic without personality defect in between attacks, may develop recognizable depressive symptoms, and responds favourably to E.C.T. Catatonic features, withdrawal, autism, aggressiveness, and negativism may occur. A mixed paranoid and depressive illness occurring after the fourth decade has been recognized for some time. It is argued that the atypical symptomatology, which may include the contrasting features of projected persecutory ideas instead of self-accusation and aggression replacing passivity, is derived from the basic personality structure. Among older patients an apparently arteriosclerotic dementia, perhaps pseudo-bulbar palsy, may be both intermittent and respond to E.C.T. In addition to the 3 "psychotic" types of atypical depression, 2 "neurotic" groups can be recognized. The first comprises obsessional states and hysteria occurring in a depressive setting. Dipsomania and the case cited by the authors in which the patient had a periodic phobia which responded favourably each time to E.C.T. are examples of obsessional forms. Hysterical or psychosomatic symptoms include focal somatic complaints or a generalized hypochondriasis with a diffuse personality change which the authors approximate to Cotard's syndrome. The second group, or *formes frustes*, includes monosymptomatic illnesses, such as insomnia, and character disorders in which symptoms such as sulkiness, negativism, and instability predominate.

The authors maintain that illnesses of this type, which are apparently unclassifiable when judged clinically, can be seen as a group of depressive illnesses in which the symptoms have been modified by the basic personality of the patient and by his intellectual status, life experience, and social milieu. Adolescence, adult life, and old age are closely related psychopathologically to the clinical expression of an illness. A threat to the ego characterizes those of adolescence and a schizophreniform illness occurs owing to poor defences. In adult life the same patient may show systematized delusions as seen in a paranoid illness, and in old age, with isolation and restriction of life, a state similar to dementia occurs. In all such patients it is of prime importance to recognize prognostic and therapeutic criteria. In a variety of case histories the authors demonstrate the syndromes they describe. E.C.T. is regarded as a specific therapy for depression and a favourable response in these patients, in their view, almost constitutes proof of diagnosis.

J. S. Bearcroft

SCHIZOPHRENIA

1013. **Study of the Somatic Preoccupations of Schizophrenics.** (Étude des préoccupations somatiques des schizophrènes)
A. Amado-Haguenauer, E. R. Glaston, M. Picard, and F. Klapahouk. *Annales médico-psychologiques* [*Ann. méd.-psychol.*] **119**, 473–500, March [received May], 1961. Bibliography.

The authors have attempted to classify somatic complaints in schizophrenic patients. They have in addition tried to ascertain their frequency, their psychopathological basis, and their course and progress in relation to the course of the illness. The group studied consisted of 30 schizophrenic patients in a female psychiatric clinic

who showed no evidence of organic impairment. A battery of investigations included a psychiatric interview, perusal of the case history, a questionary designed to elicit somatic complaints, the hypochondriasis section of the Minnesota Multiphasic Personality Inventory, the Z test (comparable to the Rorschach test), and a drawing of the human figure to indicate the organ or part believed or felt to be disordered.

Neurotic and psychotic types of somatic preoccupation are distinguished. The former includes preoccupation with sensory experiences and malfunction of an organ (nearly all patients). The psychotic type also includes general sensory experiences of a more extreme kind and complaints of partial or total disintegration of the body. The most common examples were of partial disintegration such as discontinuity, emptiness, and excision or loss of an organ (over 60% of patients). Total disintegration was less frequent and included confusion between the person and her surroundings, difficulty in sexual identification (30%), and total loss of substance.

Somatic preoccupations may express: (1) drives attaching to primary narcissism or to the oral or anal phases of development; (2) a defence against dissolution —in this case they are accompanied by other defence mechanisms such as negativeness, introspection, and projection; or (3) disintegration itself. It is believed that the frequency of somatic complaints can be used as a measure of regression. When they are found to be frequent a small degree of regression is apparent. A total absence usually betokens encapsulation and chronicity. In the early stage of the illness they are associated with primitive drives and other defence mechanisms. With further progress of the illness a diminution of somatic complaints parallels a lessening of drives and gradual disappearance of defence mechanisms. In a final stage of the illness somatic complaints, drives, and defence mechanisms are all absent. The authors conclude, agreeing with Fenichal, that disturbances of the body image are the first signs of a schizophrenic regression. *J. S. Bearcroft*

1014. **A Contribution to the Problem of So-called Reactive Schizophrenia.** (Beitrag zur Kenntnis der sogenannten schizophrenen Reaktion)
K. Rohr. *Archiv für Psychiatrie und Nervenkrankheiten* [*Arch. Psychiat. Nervenkr.*] **201**, 626–647, 1961. 35 refs.

At the University Psychiatric Clinic, Burghölzli, Zürich, 29 patients in whom severe traumatic experiences led to psychotic breakdown with a typical schizophrenic psychopathology and in whom the illness subsided after a short period were studied, a 6- to 11-year follow-up being carried out and the family history investigated. Only 2, or possibly 3, patients later developed typical schizophrenia. Five patients showed non-specific psychic abnormalities following the acute episode. Three further patients had subsequent attacks which again followed psychic trauma and were regarded as attacks of " reactive schizophrenia ". In about half the cases the patient remained normal throughout the follow-up period. The family histories appeared to show a lower incidence of schizophrenia than in the case of true schizophrenics, but the figures were too small to allow definite conclusions to be drawn.

From these findings the author concludes that reactive schizophrenia—although psychopathologically identical with schizophrenia—is a separate entity which is neither identical with schizophrenia nor something entirely different from it. The prognosis includes the possibility of a chronic course after relapses, but such an outcome does not occur with the same frequency as in schizophrenia. *J. Hoenig*

1015. **Stabilization of a Human Blood Factor Causing Behavior Changes in Rats**
J. R. Bergen, C. Saravis, R. B. Pennell, and H. Hoagland. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] **2**, 201–204, April, 1961. 12 refs.

It has been shown that the globulin fraction of schizophrenic blood is capable of producing transient psychotic episodes in healthy people, and that globulin fractions produce behaviour changes in trained rats. In this investigation reported from the Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts, samples of blood were obtained from healthy and schizophrenic patients and processed simultaneously to produce protein globulin precipitate and soluble plasma protein solution. Fractions were then tested in rats by the delay they caused in a standardized climbing test.

Control of the environment in which the isolated fractions were kept was rigorous. It was found that the extreme lability of the protein extracts was intimately related to oxidative processes. The authors state that the active substance is probably not a protein, but a small molecule firmly bound to protein which is maximally associated with a globulin fraction. It was also found that the oxidative processes could be reversed when the fractions were kept in an atmosphere of hydrogen.

[Final isolation of this active substance may be an important step in clarifying the aetiology of schizophrenia.] *B. M. Davies*

TREATMENT

1016. **A Comparative Study of Antidepressants in Balanced Therapy**
D. C. English. *American Journal of Psychiatry* [*Amer. J. Psychiat.*] **117**, 865–872, April, 1961. 1 fig., 14 refs.

As part of a larger study of private psychiatric patients in Jackson, Michigan, evidence is presented that the treatment of depressed patients with isocarboxazid (ICZ) plus a phenothiazine is more effective than the use of a phenothiazine and any one of 7 other antidepressants (phenelzine, iproniazid (INZ), imipramine, nialamide, phenyl*cyclo*propylamine, deanol, and benactyzine–meprobamate). Of 195 depressed patients, 91% were " rehabilitated " after 3 to 15 days' treatment with ICZ; this was the only result to equal that of electric convulsion therapy (E.C.T.), which effected " rehabilitation " in 90% of 842 patients after 5 to 30 days' treatment. ICZ was started in a dosage of 10 mg. thrice daily, and this

was reduced according to improvement. All patients were followed up for a minimum of 4 weeks.

Similarly, in acute schizophrenic reactions ICZ used in combination with a phenothiazine was the only antidepressant to approach the efficacy of E.C.T.—80% of 51 patients being "rehabilitated" with the former compared with 89% of 168 with the latter—and was excelled only by ICZ and INZ together, with which 86% of 21 patients were "rehabilitated".

Discussing the rationale for "balanced therapy"—the combination of an antidepressant and a phenothiazine—the author points out that INZ and ICZ have a double action: a rise in serum serotonin (5-HT) levels associated with initial tranquillization and a later increase of noradrenaline release which correlates with elevation of mood. The tranquillizing action potentiates, and can be reinforced by, the addition of a phenothiazine, which serves both to reduce excessive agitation and any subsequent overstimulation. Paradoxically, in cases where large doses of phenothiazines have failed to control extremely disturbed behaviour control may be achieved by adding ICZ. A possible explanation is that where phenothiazines have produced almost complete noradrenaline blockade ICZ can only result in raising the serum 5-HT level, with consequent reserpine-type tranquillization.

The incidence of toxicity and serious side-effects was very low and drugs never had to be withdrawn. Hypotension was minimized by giving divided doses after meals. Concern over hepatotoxicity, in particular, seems unwarranted since the serum alkaline-phosphatase levels, determined bi-weekly in all patients, rose in only 3 cases. In 2 of these the level returned to normal within 2 weeks, despite continuation of drug therapy; the third patient developed a mild hepatitis 4 weeks after the start of chlorpromazine therapy, and 5 days after ICZ was substituted for INZ. Although ICZ was continued (minimal symptoms, suicidal risk) the patient improved clinically, with remission of jaundice by the 7th day.

[There is no statistical handling of any treatment comparisons. It is not always clear which group of patients the author is writing about or the exact treatment they are receiving. Several totals do not appear to tally.]

Alan A. Black

1017. **Combined Drug Therapy of Chronic Schizophrenics. Controlled Evaluation of Placebo, *dextro*-Amphetamine, Imipramine, Isocarboxazid and Trifluoperazine Added to Maintenance Doses of Chlorpromazine**
J. F. Casey, L. E. Hollister, C. J. Klett, J. J. Lasky, and E. M. Caffey Jr. *American Journal of Psychiatry* [*Amer. J. Psychiat.*] **117**, 997–1003, May, 1961. 29 refs.

A large-scale cooperative study designed to explore the possible enhancement of conventional treatment of chronic schizophrenia by the addition of the newer antidepressant drugs was carried out at U.S. Veterans Administration hospitals, in which 462 men with chronic schizophrenia took part. All had been on maintenance doses (200 to 600 mg. daily) of chlorpromazine for at least 2 months without improvement. The patients were divided into groups each of which received one of the following preparations (maximum daily dose indicated) in addition to the chlorpromazine: D-amphetamine (60 mg.), isocarboxazid (30 mg.), trifluoperazine (30 mg.), imipramine (225 mg.), and placebo, a double-blind procedure being used. The symptomatic response was studied by means of 2 scales—an interview scale (In-patient Multidimensional Psychiatric Scale) and a ward scale (Psychotic Reaction Profile).

By the end of 20 weeks all groups except that taking D-amphetamine and chlorpromazine had improved, the general improvement being the same for all groups, including that receiving the chlorpromazine–placebo combination. None of the combinations was superior to chlorpromazine and placebo. Trifluoperazine with chlorpromazine increased the prevalence of extrapyramidal syndromes. All groups except that given D-amphetamine had increased appetite with gain in weight, this being most marked in the groups receiving imipramine and isocarboxazid additions respectively.

The authors comment that, "although the present study did not demonstrate substantial benefit from combined therapy, the chronicity of the patients and the method of drug administration limit generalization".

E. H. Johnson

1018. **Chlorprothixene ("Truxal") Compared to Chlorpromazine.** [In English]
J. Remvig and L. M. Sonne. *Psychopharmacologia* [*Psychopharmacologia (Berlin)*] **2**, 203–208, 1961. 4 refs.

In a clinical trial carried out at the University Psychiatric Clinic (Rigshospitalet), Copenhagen, the effects of chlorprothixene ("truxal") were compared with those of chlorpromazine in various "acute" psychiatric disorders. Altogether, 163 patients completed the trial. The drugs were administered in identical capsules in what were considered to be comparably effective doses. The method of administration was "blind".

The results suggest that amongst the "relatively" acute psychotic, hyperactive, and agitated patients the results with chlorprothixene were equal to those with chlorpromazine. In general the side-effects of the drug were similar to those of chlorpromazine.

[The authors do not detail the criteria by which improvement was judged and, owing to the methodology adopted, the patients did not act as their own controls. It would appear also that the patients were not matched for any items except that they suffered from similar illnesses.]

N. Rathod

1019. **The Therapeutic Axis-syndrome of Neuroleptic Drugs and its Relation to Extrapyramidal Symptomatology.** (Das therapeutische Achsensyndrom neuroleptischer Medikamente und seine Beziehungen zu extrapyramidaler Symptomatik)
H. J. Haase. *Fortschritte der Neurologie, Psychiatrie und ihrer Grenzgebiete* [*Fortschr. Neurol. Psychiat.*] **29**, 245–268, May, 1961. 6 figs., bibliography.

The frequent occurrence of extrapyramidal symptoms during treatment with neuroleptic drugs has been given various and partly conflicting explanations. The present author has investigated 200 psychiatric in-patients at the

Delaware State Hospital, Farnhurst, to obtain further evidence for his hypothesis—put forward already in previous publications—that certain extrapyramidal modifications of fine movements are essential indicators of an effective therapeutic action of neuroleptics.

The author had previously found that of 45 patients treated with chlorpromazine, 86% showed an extrapyramidal inhibition in their handwriting, whereas in the remaining 14% either the conditions for writing were insufficient or the dose of chlorpromazine was too small to be clinically effective. In the present series the patients were variously receiving chlorpromazine, prochlorperazine, trifluoperazine, fluphenazine, and thioperazine and a total of 1,200 handwriting samples were collected under constant conditions before, during, and after treatment and analysed for the characteristic disturbances —diminished obliquity to the right, diminution in letter-size, and stiffening and narrowing of the handwriting. These changes were observed in practically all patients provided they were receiving an optimally effective dose of the neuroleptic. Whereas only a small proportion of patients showed such typical extrapyramidal symptoms as reduction or loss of automatic movements, such as swinging the arms when walking, most patients showed some degree of impoverishment of motor spontaneity and slowing down of motor patterns. This extrapyramidal hypokinesis or akinesis is related on the psychological side to a dampening of impulse. Thus it is the diminution of psychokinetic impulses which represents the therapeutic effect. Clinically, this is not only evident in respect of psychomotor excitement, but also in states of affective tension where apparently inactive schizophrenic patients are, in fact, tensely absorbed in delusions or hallucinatory experiences; the reduction of psychokinetic impulse is clinically manifest as affective relaxation, which allows the patient to use his energy in a more normal way.

The author regards as a further manifestation of the psychokinetic inhibitory action of neuroleptics the diminution in the production of psychotic experiences, particularly paranoid-hallucinatory ones, but usually only in so far as they are closely linked with affective tension. This effect, however, is non-specific and applies to psychotic experience production of every possible origin. He regards the following extrapyramidal symptoms as being not related, or only negatively related, to the therapeutic effect: (*a*) dyskinetic reactions, such as torticollis spasticus, which mainly occur with neuroleptics having a particularly strong affinity to the extrapyramidal system; (*b*) rigor, observed under similar conditions; (*c*) akathisia or hypokathisia (inability to sit still); and (*d*) tremor. All these coarse extrapyramidal disturbances retard rather than promote the therapeutic effect of the neuroleptics. On comparing the effects of chlorpromazine with equivalent doses of prochlorperazine, trifluoperazine, fluphenazine, and thioperazine it was found that the smaller the therapeutically effective dose of the drug, the higher is its affinity to the extrapyramidal system. Symptoms sometimes observed during treatment with neuroleptics which are independent of extrapyramidal hypokinesis and yet, at times, therapeutically desirable are: (*a*) somnolence (usually found in the initial phase of treatment); (*b*) mild non-specific general sedation; (*c*) mild euphoria following the reduction or interruption of the medication; and (*d*) gradual decline of therapeutic effectiveness despite unaltered dosage.

The author proposes the use in this connexion of the term "extrapyramidal psychokinetic regulation syndrome" in place of "Parkinsonism", as the latter not only comprises a much wider range of extrapyramidal symptoms and only refers to somatic data, but also is established as a pathological entity. *H. H. Grosser*

1020. **Single Daily Dose Treatment of Psychiatric Patients with Phenothiazine Derivatives**
F. J. ROBERTS. *Journal of Mental Science* [*J. ment. Sci.*] **107**, 104–108, Jan. [received March], 1961. 10 refs.

Over a period of 9 months 86 psychiatric patients (82 male and 4 female, aged 18 to 80 years) at St. Luke's Hospital, Middlesbrough, were given a single daily dose of trifluoperazine ("stelazine"), beginning with 2 mg. parentally or not less than 10 mg. by mouth, increased to the effective dose for each patient by an additional 5 mg. on alternate days. The average effective dose was 25 mg., range 10 to 45 mg. The diagnoses were: acute schizophrenia (5 patients), chronic schizophrenia (56), epilepsy (3), endogenous depression (5), withdrawal symptoms of addiction (5), mania (2), toxic psychosis (3), senile states (5), obsessional neurosis (1), and traumatic dementia (one patient). The duration of stay in hospital varied from 2 weeks to 19 years (average 7 years) and duration of symptoms from one week to 20 years (average 2½ years). The results of treatment were considered to be "very good" (return home with great reduction of symptoms) in 23 cases, "good" (return home and attending the Day Hospital, or going to work from hospital) in 28, and "fair" (able to work in hospital) in 29 cases. Some of the patients received other treatment in addition to trifluoperazine—namely, anticonvulsant drugs in the epileptics and 4 patients with chronic schizophrenia; imipramine and electric convulsion therapy (E.C.T.) in 4 endogenous depressives; and E.C.T. in 3 patients with acute and 8 with chronic schizophrenia.

The author states that the advantages of the one (evening) administration were a saving of from ¾ of an hour to 2 hours of nursing time a day in each ward, a feeling on the part of the patient of lessened dependence on tablets, and, if the patient was out in the community, cessation of fear of ridicule when seen taking tablets by workmates. The incidence of side-effects, including Parkinsonism, was 14% compared with 45% and 66% in two previously reported series. *G. de M. Rudolf*

1021. **Oral Sernyl in Obsessive States**
B. M. DAVIES. *Journal of Mental Science* [*J. ment. Sci.*] **107**, 109–114, Jan. [received March], 1961. 4 refs.

It has been shown that "sernyl" (phencyclidine) intravenously produces a less severe and short-lasting disturbance than lysergic acid diethylamide. The present author reports the results obtained with phencyclidine by mouth in capsule form in 5 patients with obsessional illnesses at Bethlem Royal Hospital, London, 5 to 15

mg. of the drug being given before a total of 73 interviews. Experience showed that 15 mg. was too large a dose, producing severe side-effects, and that 10 mg. was sufficient. The patient had a light meal only, the capsules being given 30 minutes before the interview. The onset of symptoms varied from 30 to 60 minutes and persisted for 1 to 3 hours. The cases are described in detail. In one case, that of a woman aged 21 who had been ill for 4 years, there was no improvement after 20 interviews, but in another case, in which the illness had also been present for 4 years, there was improvement after only 10 interviews. The drug appeared to be of value in assisting psychotherapy. *G. de M. Rudolf*

1022. **A Monoamine Oxidase Inhibitor (Niamid) in the Treatment of the Mentally Subnormal**
T. S. DAVIES. *Journal of Mental Science* [*J. ment. Sci.*] **107**, 115–118, Jan. [received March], 1961.

At Llanfrechfa Grange Hospital, Newport, Monmouthshire, " niamid " (nialamide) was tried in the treatment of certain types of mentally subnormal patients. The ages of the patients ranged from 4 to 70 years and the I.Q. from 25 to 80. The drug was given in a dosage of 30 to 150 mg. daily, except in one patient who received 300 mg. a day for several months without ill effect.

Epileptics (21) became less moody and quarrelsome, but the drug had no effect upon the frequency or severity of the fits. Some improvement was observed in 3 out of 5 patients with post-encephalitic Parkinsonism. Of the 27 mongols, 4 apathetic males showed a much greater interest in their surroundings after administration of nialamide and of 16 females, 15 improved, one of them, who had never spoken, being able to speak in short sentences. Of 50 psychopaths, 34 improved, becoming more cooperative and more adult, especially the females. The 12 hemiplegics and diplegics did not benefit to any marked degree; in fact they became more aware of their physical handicaps and so more unhappy. Similarly, there was no benefit in 5 infantile psychotics, who became more overactive. The drug unmasked delusions causing exacerbation of symptoms in some schizophrenics but it increased activity in anergic cases. Of 2 patients with phenylpyruvic oligophrenia, one became worse and the other showed no change.

A side-effect encountered was an increase in tension and agitation amounting almost to hypomania. The author states that the overactivity can be reduced by administration of the drug in combination with chlorpromazine. *G. de M. Rudolf*

1023. **An Objective Assessment of the Effects of Nialamide on Depressed Patients**
J. INGLIS, W. K. CAIRD, and R. B. SLOANE. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **84**, 1059–1063, May 13, 1961. 20 refs.

Writing from the Department of Psychiatry, Queen's University, Kingston, Ontario, the authors stress the importance of homogeneity in selecting psychiatric patients for clinical trials. They point out that depressive features may be present in various psychoses and psychoneuroses and that apparent effectiveness of a drug may really be an expression of the self-limiting nature of the illness. They suggest that the placebo reaction has been insufficiently studied in some reports on nialamide. As clinical assessment is imprecise, the authors' scheme was designed to be as objective as possible.

There were two groups of 13 patients, one receiving nialamide and the other an inert preparation in 50-mg. doses thrice daily. The patients were all sufficiently depressed to need hospital admission, and electric convulsion therapy (E.C.T.) would have been used in the pre-drug era. The diagnoses were manic depressive and psychoneurotic depression. The observers did not know which treatment a patient was having. Routine liver function and blood tests were made and the blood pressure was regularly taken. Mood, cognition, and psychomotor function were determined by standard psychometric tests. Impression of sickness was rated by the psychologist and by the resident and consulting psychiatrists independently, none of them knowing the results of the tests. This impression was simply rated " improved " or " unimproved ". After a 3 weeks' trial " unimproved " patients were given E.C.T., and all but one of them improved.

The authors found no significant difference between the drug-treated and the placebo groups, and conclude that nialamide had no noticeable effect in treating psychiatric depression. *Gavin Thurston*

1024. **A Preliminary Report on Hypnosis as an Anesthetic Agent in Electroconvulsive Therapy with Succinyl Choline**
A. WEINBERG, L. CAMMER, and S. DELL'ARIA. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] **2**, 178–182, April, 1961. 5 refs.

Hypnosis was tried as the primary anaesthetic agent for electric convulsion therapy on 58 patients at Gracie Square Hospital, New York. Rapid induction is necessary and the following method has been found most useful. The room is well lit and soft music is played. The patient then lies comfortably and is asked to listen intently to the tones of his various breath sounds. He is then told to close his eyes and to imagine that he is seeing the respiratory movements of his body and that as he visualizes these he will enter into a deep, pleasant, relaxed state. Further suggestions are made and it is said that the induction phase takes about 2 to 5 minutes. The depth of hypnosis is indicated by deep, regular breathing, production of arm flaccidity, inability to open the eyelids, and hypalgesia of the arm. Further details of the method are given. The authors found that only one of the 58 patients could not be hypnotized and that additional barbiturate anaesthesia was needed in only 10% of 140 inductions. It is suggested that where barbiturate anaesthesia is contraindicated hypnosis with a relaxant provides a simple, safe, and valuable technique that needs to be further investigated. *B. M. Davies*

1025. **Treatment of Mental Disorders with Frontal Stereotaxic Thermo-lesions: a Follow-up Study of 116 Cases.** [Monograph, in English]
T. HERNER. *Acta psychiatrica et neurologica Scandinavica* [*Acta psychiat. scand.*] **36**, Suppl. 158, 140, 1961. 16 figs., bibliography.

Dermatology

1026. **Efficacy of Cyproheptadine as an Antipruritic Agent: a Preliminary Report**
A. L. WELSH and M. EDE. *Journal of New Drugs* [*J. New Drugs*] **1**, 22–27, Jan.–Feb., 1961. 3 refs.

The antipruritic effect of cyproheptadine, which is 1-methyl-4-(5-dibenzo-(*a*:*e*)-*cyclo*heptatrienlidene) piperidine hydrochloride, was tested on 311 patients, ranging in age between 9 months and 87 years, suffering from various dermatoses. The drug was given by mouth in a dose of 2 to 20 mg. daily, the average duration of therapy being 41 days. To 166 of these patients trimeprazine, rauwolfia, or chlorprophenpyridamine maleate had previously been given as an antipruritic agent, and the recorded results obtained with this therapy were used as a control.

Relief of pruritus estimated to be between 75% and 100% was obtained with cyproheptadine in 246 (79·1%) of the 311 patients, between 50% and 74% in 37 (11·8%), and under 50% in 28 (9%). The equivalent figures for the 166 control cases were 83 (50%), 65 (39·1%), and 18 (10·8%).

The only side-effects noted during cyproheptadine therapy were drowsiness, somnolence, or lethargy in 3 cases, in only one case severe enough to necessitate cessation of treatment, and headache in 2 cases, representing an incidence of 1·6%. These side-effects were readily reversible on withdrawal of the drug. The side-effects among the 166 patients treated with other antipruritic agents had totalled 186, an incidence of 112·7%, each of the 3 drugs causing an approximately equal incidence of side-effects.

Investigations carried out after 2 weeks and again at the end of 3 and 6 months of cyproheptadine therapy showed no noticeable variation in blood count, the results of urine analysis, or in blood pressure or pulse rate. The authors conclude that their results appear to warrant further investigation of the drug.

E. H. Johnson

1027. **The Local Treatment of Rosacea**
C. M. BUNCKE, J. O'D. ALEXANDER, and G. HARVEY. *Scottish Medical Journal* [*Scot. med. J.*] **6**, 112–115, March, 1961. 2 refs.

Clinical trials at the Royal Infirmary, Glasgow, have shown that an ointment consisting of 2 or 3% of precipitated sulphur, salicylic acid, and "quinolor" compound (chlorhydroxyquinoline) ointment in a base consisting of 2 parts of "eucerin" (wool alcohol ointment) and one part of water, to be very effective in rosacea. Severe irritation occurred in a few cases, but on the whole the ointment was well tolerated. An ointment containing 0·5% benzoyl peroxide (a constituent of quinolor ointment) in a similar base was not so useful, but caused little irritation. The authors consider both ointments to be far superior to any other local remedies for rosacea.

E. W. Prosser Thomas

1028. **A Dermatological Survey of Long-stay Mental Patients**
C. B. KIDD and J. C. MEENAN. *British Journal of Dermatology* [*Brit. J. Derm.*] **73**, 129–133, April, 1961. 16 refs.

A survey of skin diseases in mental illness was carried out on 1,700 long-stay patients at Purdysburn Hospital, Belfast, the object being "to define the occurrence of psychocutaneous lesions in a mentally ill population and to assess the skin diseases associated with the infective and dietetic hazards peculiar to institutional life". Patients who had been in the hospital for at least a year since the date of their last admission were selected, and in two days every unit of the hospital was visited and details obtained of the age, sex, and date of admission of the patients and the psychiatric diagnosis. The patients were then examined and all skin lesions noted and classified according to the method of Hall and Burrows (*Brit. J. Derm.*, 1957, **69**, 400).

The three largest psychiatric groups were schizophrenia, mental deficiency, and arteriopathic disorders. Of the 1,700 patients, 413 (24%) had skin affections. Traumatic skin disorders constituted the largest group (114), but it included 53 cases of tatooing. Next came seborrhoeic disorders (73), half of which were of acne vulgaris, followed by simple neoplastic conditions (70). There were no cases of scabies. The neurodermatitis group, selected according to Becker and Obermayer, contained 13 cases—rosacea (7), vitiligo (4), and neurodermatitis and alopecia areata (one of each). Lichen planus was not observed, and cases of pruritus and simple excoriation were not included in the survey.

Attempts to correlate the occurrence of skin diseases with the psychiatric diagnosis showed a broad spread of no statistical significance; this was particularly true for psoriasis, the 34 patients being representative of most common types of mental illness. There was only one case of skin disease due to avitaminosis.

The authors conclude that these patients are representative of the mentally ill in a large urban population, that the dermatological problems of mental hospital patients differ little from those in the general population, and that mental stress is a factor in, rather than the cause of, the neurodermatosis.

F. E. Kenyon

1029. **Studies in Contact Dermatitis. XII. Sensitivity to Oleyl Alcohol**
C. D. CALNAN and I. SARKANY. *Transactions of the St. John's Hospital Dermatological Society* [*Trans. St John's Hosp. derm. Soc. (Lond.)*] No. 44, 47–50, 1960 [received April, 1961]. 7 refs.

As part of continued studies of lipstick dermatitis the authors have investigated 3 cases in which the reaction was to the lipstick base. These patients were found to be sensitive to oleyl alcohol, which is used in the high-

indelibility range of products to replace the gelled castor oil used in ordinary ranges. Allergy to alcohol is rare, but has been reported even to the ethyl form. The manufacturers have suggested that these sensitivities are due to impurities in the chemicals used, but such a theory is, of course, hard to prove. *Allene Scott*

1030. **New Therapeutic Agent for Tinea Versicolor—9-Aminoacridinum 4-Hexylresorcinolate**
E. H. ZIMMERMAN. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **176**, 23–25, April 8, 1961. 1 fig., 4 refs.

Tinea versicolor is considered to be easy to diagnose but difficult to cure; neither local application of medicaments nor griseofulvin by mouth has proved to be of much value.

The present author describes a trial of 9-aminoacridinium 4-hexylresorcinolate in the treatment of this condition. The drug is antibacterial and antifungal *in vitro*, and studies in animals have shown that it has low systemic toxicity, low sensitizing potential, and is non-irritating to skin and conjunctivae. It was used as a lotion containing 2 mg. per ml. of propylene glycol, a cream containing 2 mg. per gramme of a water washable base, and an aerosol spray containing 10 mg. in each 150-g. dispenser on 40 patients in whom the condition was diagnosed clinically and by microscopical examination of skin scrapings. The majority of the patients had suffered from the disease for 2 to 3 years, and many had not responded to treatment with other agents or had had a relapse after treatment. The patients applied the medication daily after a bath or a shower, and continued to do so for one to 2 weeks after clinical and microscopical disappearance of the fungus. Treatment lasted 4 to 8 weeks and after completion follow-up examinations, clinical and microscopical, were carried out at 2- to 4-week intervals. Of the 40 patients, 34 showed excellent results within 4 to 8 weeks and all except 2 of these remained clear of infection for 8 to 15 months. In 2 patients there was a mild recurrence 6 and 10 months respectively after completion of treatment, and the condition subsequently responded to re-treatment for 3 weeks. Of the remaining 6 patients, 5 showed a good response 4 to 6 weeks after starting treatment, but infection recurred within 2 to 5 months; these 5 patients responded to a further course and remained clear during a follow-up period of 6 to 9 months. One patient in the series did not respond in spite of three courses of treatment.

The preparations were also used on 26 patients with dermatophytoses due to *Trichophyton rubrum*, *Epidermophyton inguinale*, *T. mentagrophytes*, and *Microsporum audounii*, and on 10 patients with various types of pyoderma. In these conditions the preparations of 9-aminoacridinium 4-hexylresorcinolate were consistently poor in effect and in some cases there was a flare-up of the eruptions.

The three preparations were equally efficacious and no allergic reactions were observed. The author concludes that this treatment is more effective than any previously used for infection due to *Malassezia furfur*.

P. T. Main

1031. **Studies in the Epidemiology of Tinea Pedis. VI. Tinea Pedis in a Boys' Boarding-school**
M. P. ENGLISH, M. D. GIBSON, and R. P. WARIN. *British Medical Journal* [*Brit. med. J.*] **1**, 1083–1086, April 15, 1961. 11 refs.

The incidence of tinea pedis was investigated at a boys' school with about 200 boarders aged 7 to 18 years. There were no bathrooms, but all boys took a morning shower twice a week and used the same shower-baths after games. The school's swimming-bath was open only in summer and organized visits took place once or twice a week, though senior boys were not restricted in their use of the bath. The ban on visits to public baths did not extend to the 150 day-boys, however, who also used the school's swimming-bath.

Two visits were paid to the school, one in October, 1958, and the other in June, 1959. At the first visit 52% of the boys were found to have lesions, but only 22% were shown to be infected with dermatophytes. At the second visit 68% had lesions and 18% were infected, but no single direct relationship between lesions and infection could be noted. The *interdigitale* type of *Trichophyton mentagrophytes* was the most important causal fungus, but *T. rubrum* was also isolated at the first visit. Of 11 lesion-free carriers seen at the first visit, only one was still carrying the fungus on lesion-free feet 8 months later, suggesting that true carriers are rare.

R. R. Willcox

1032. **Studies in the Epidemiology of Tinea Pedis. VII. The Circulation of Infection**
M. P. ENGLISH. *British Medical Journal* [*Brit. med. J.*] **1**, 1086–1089, April 15, 1961. 3 figs., 22 refs.

As shown in earlier papers in this series (*Brit. med. J.*, 1959, **1**, 1442, 1446; 1960, **1**, 1860; 1960, **2**, 573, 577; 1961, **1**, 1083; *Abstr. Wld Med.*, 1960, **27**, 73; 1960, **28**, 485; 1961, **29**, 115, 116; and Abstract 1031 above), *Trichophyton mentagrophytes* is the most common cause of tinea pedis in Bristol. In boys aged 11 to 14 years in local-authority day-schools the incidence of infection was found to be about 6·5% and cross-infection usually took place in the local swimming-bath. In a boarding-school with a more communal life and a greater emphasis on sport the incidence was about 12%. Day-school boys seldom contracted infection from their families, but there was a higher rate of cross-infection in families from which boarding-school boys were drawn; proportionally more boys from higher social classes attended universities, where the incidence was again high amongst students, especially those living in hostels. Girls were less commonly infected, the incidence in those attending day-schools averaging 1·6%. After leaving school more boys than girls join sports and swimming clubs; also at the time the investigations were carried out the boys were liable to national service. All these are situations in which cross-infection with tinea pedis is likely to occur, so that also as young adults males are more exposed to infection than females.

Infections with *T. rubrum* were less common. Cross-infection within the family was considered the most important method of spread, and as infection by this fungus

is more resistant to treatment than that due to *T. mentagrophytes* the family in which there is an infected person is exposed to risk over a longer period. In a number of cases the infection was obviously contracted during residence abroad. The incidence of *T. rubrum* infection did not seem to be particularly associated with any social group.

The importance of outside sources of infection in the case of both fungi is stressed, and it is considered that it should be possible to trace the routes by which tinea pedis is circulated in a given locality. *R. R. Willcox*

1033. **The Neurodermatoses and Intelligence**
C. B. KIDD and J. C. MEENAN. *British Journal of Dermatology* [*Brit. J. Derm.*] 73, 134–136, April, 1961. 11 refs.

It is suggested that if " psychocutaneous " diseases represent somatization of stress response, then a low incidence would reasonably be expected in defectives and their occurrence should correlate with the severity of the mental defect, since subjects of low intelligence do not readily repress emotion. At Purdysburn Hospital, Belfast, 700 defectives were examined for evidence of the neurodermatoses, the classification of Becker and Obermayer being used, except that pruritus and simple excoriation were excluded.

It was found that 17 (2·4%) of the patients (10 males and 7 females) had a neurodermatosis—vitiligo in 5, alopecia areata in 5, rosacea in 4, lichen simplex chronicus in 2, and lichen planus in one. The psychiatric classification was moron (I.Q. 70 to 50) 5 patients, imbecile (I.Q 50 to 20) 9, and idiot (I.Q. less than 20) 3. There was no correlation between the occurrence of the neurodermatosis and age, psychiatric category, or level of intelligence. Further, the ratio of males to females and the over-all incidence of the neurodermatoses in the defective population studied did not essentially differ from that observed in the general population.

It is concluded that these findings lend support to the view that psychological factors are not of over-riding importance in the aetiology of the neurodermatoses.

F. E. Kenyon

1034. **Psychosomatic Aspects of Rosacea**
F. A. WHITLOCK. *British Journal of Dermatology* [*Brit. J. Derm.*] 73, 137–148, April, 1961. 10 refs.

The psychosomatic aspects of rosacea were studied at Newcastle General Hospital, Newcastle upon Tyne, in 50 patients (20 male and 30 female) who were interviewed, particular attention being paid to social relationships and the presence or absence of anxiety in social situations. The interview was supplemented by the Maudsley Medical Questionnaire, to which 6 questions were added. A group of 50 controls from among patients attending a dermatological out-patient clinic for a variety of skin diseases and matched for age and sex were similarly interviewed.

Of the 20 males with rosacea, 10 were classified as psychiatrically normal, 6 showed anxiety symptoms, 2 had mild obsessional features, one was an epileptic, and one an alcoholic. Only in 2 cases was the onset of the rosacea related to emotional trauma. Of the male controls, only 6 were psychiatrically normal, while 3 showed emotional precipitation of the dermatoses. As regards the females with rosacea 22 were psychiatrically normal, 7 showed anxiety symptoms, and one was a borderline defective. The onset of rosacea was related to emotional trauma in 6 cases. Of the 30 female controls, 17 were normal.

Analysis of the replies to the questionary showed that over-all scores of male and female patients with rosacea did not differ significantly from those of the controls. Social anxiety symptoms were not peculiar to rosacea patients when compared with other dermatoses; there was thus no specific " rosacea personality " and the features described by other workers are considered to be general features of neuroticism. In the 8 cases in which psychological factors were important in causation two emotions were prominent—a sense of social shame and feelings of resentment and injustice. Blushing easily was more frequent in the controls than in the patients.

It was concluded that " rosacea is a non-specific reaction precipitated by a variety of stimuli and that only in a minority of patients could psychological factors be considered of importance ". *F. E. Kenyon*

1035. **The Treatment of Acne Vulgaris with Tolbutamide**
F. R. BETTLEY. *British Journal of Dermatology* [*Brit. J. Derm.*] 73, 149–151, April, 1961. 6 refs.

A double-blind trial of tolbutamide, sulphamethoxypyridazine, and a placebo in the treatment of 30 cases of acne vulgaris was carried out at the Middlesex Hospital, London. Each drug was administered for a period of one month. Of the 30 patients, 13 showed improvement with tolbutamide, 16 with sulphamethoxypyridazine, and only 7 with the lactose placebo.

The author states that the response to tolbutamide was independent of that to sulphamethoxypyridazine; of the 16 patients showing improvement with the latter drug, 6 were improved and 10 not improved with tolbutamide. Further study is necessary to determine whether tolbutamide has a place in the treatment of acne.

John T. Ingram

1036. **A Simple Prophylactic Treatment for Hyperhidrosis of the Feet.** (Простейший способ профилактики потливости ног)
A. N. VOLKOV. *Вестник Дерматологии и Венерологии* [*Vestn. Derm. Vener.*] 35, 72–73, March, 1961.

The author describes a method of treatment for hyperhidrosis of the feet which he has used successfully for 10 years. The formula of the solution used is as follows: formalin 30 parts, aluminium alum 0·5 parts, 96° spirit 90 parts, and urotropin 1 part. The feet are washed and dried, and the solution applied with cotton-wool, especially thoroughly between the toes. If any cracks or wounds are present, these ought to be treated first by soaking in potassium permanganate. One application only is sufficient to keep the feet dry for 15 to 30 days. More than 400 patients have been successfully treated by this method. The solution may also be used for hyperhidrosis of the axillae, when it should be diluted with an equal amount of water. *N. Hopewell*

Paediatrics

1037. **A Milk Mixture with Fat Content Resembling That of Human Milk for Routine Feeding of Young Infants.** (Eine dem Fettgehalt der Frauenmilch angeglichene Normalnahrung für junge Säuglinge)
J. JOCHIMS. *Deutsche medizinische Wochenschrift* [*Dtsch. med. Wschr.*] **86**, 851–854, April 28, 1961. 1 fig., 6 refs.

The author reports, on the basis of 2 years' clinical experience, favourable results in the feeding of premature and newborn infants with two enriched cow's milk preparations which contained the same proportion of fat as human milk. The feeds were prepared from cow's milk diluted either to one-half or to two-thirds, to which was added lactose to a concentration of 4% and 2% fat, the added fat being either butter or a vegetable fat (" mondamin "). No difference could be detected between the two different products, as judged by the progress of the infants fed one or other of these preparations.

John Lorber

1038. **Cow's Milk Fat and Vegetable Fat in the Feeding of Healthy Young Infants.** (Kuhmilchfett und pflanzliches Fett in der Ernährung des jungen, gesunden Säuglings)
W. DROESE and H. STOLLEY. *Deutsche medizinische Wochenschrift* [*Dtsch. med. Wschr.*] **86**, 855–860, April 28, 1961. 10 figs., bibliography.

From the University Paediatric Clinic, Munich, are reported the results of a trial on 32 healthy infants who received during the first 3 months of life one of the following milk feeds: (1) the " traditional " one-half or two-thirds diluted cow's milk with added sugar; (2) the " American " formula consisting of unsweetened evaporated milk reconstituted to four-fifths strength; and finally (3) Feed 1 with the addition of 2% vegetable (cottonseed) oil. Subsequent intake and output studies, records of gain in body weight, and electrolyte balance studies showed that infants on the fat-enriched milk (Diet 3) did better than those on the other two diets.

John Lorber

NEONATAL DISORDERS

1039. **Effect on Bilirubin Metabolism in the Newborn of Sulfisoxazole Administered to the Mother**
H. I. KANTOR, D. A. SUTHERLAND, J. T. LEONARD, J. H. KAMHOLZ, N. D. FRY, and W. L. WHITE. *Obstetrics and Gynecology* [*Obstet. and Gynec.*] **17**, 494–500, April, 1961. 1 fig., 35 refs.

The authors of this paper from St. Paul's Hospital, Dallas, Texas, had previously found sulphafurazole (sulfisoxazole, " gantrisin ") a useful drug in the prevention of amniotic infection when labour was delayed following rupture of the membranes. Disturbed by the recent evidence that sulphonamides administered to newborn premature infants may increase the risk of kernicterus, they investigated the effect of maternally administered sulphafurazole on the bilirubin metabolism of the newborn child and present the results of estimations of free and conjugated serum bilirubin in 278 normal infants, 44 of whose mothers had been treated with sulphafurazole. The dosage of the drug was: 4 g. initially, 2 g. 4 hours later, and then 1 g. 6-hourly until delivery.

In the 234 infants whose mothers had been untreated free and conjugated bilirubin levels were estimated on cord blood and, in about a quarter of them, on specimens taken at one and 2 days old. Statistical analysis indicated that there were no significant differences between the results in those infants who had the same ABO or Rh (D) groups as their mothers and in those whose blood groups were different.

In the 44 infants of treated mothers, in which group most of the readings were made at one and 2 days as well as on cord blood, the conjugated bilirubin levels did not differ significantly from those of the controls, but the free bilirubin levels were distinctly lower. The maternal bilirubin levels were unchanged during the course of the treatment. Cord-blood levels of free sulphafurazole were about two-thirds of the maternal levels at delivery, but elimination of the drug was almost complete after 2 days.

The authors suggest that the lower free bilirubin in the " treated " cases was due to preferential binding of sulphonamide to serum albumin and a consequent transfer of bilirubin to the tissues—a situation which could be dangerous if the free bilirubin levels were abnormally high. They briefly mention current views on the metabolism of bilirubin in the newborn infant and emphasize that the level of free bilirubin in the serum may not reflect the tissue level, owing to variations in the bilirubin-binding capacity of the blood. They suggest that in normal infants there is no evidence that maternally administered sulphafurazole adversely affects the child, but that sulphonamides or other drugs causing albumin–bilirubin dissociation should not be given if there is reason to anticipate that the child might be abnormally jaundiced after birth.

E. G. Hall

1040. **Novobiocin and Neonatal Hyperbilirubinemia—an Investigation of the Relationship in an Epidemic of Neonatal Hyperbilirubinemia**
J. M. SUTHERLAND and W. H. KELLER. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **101**, 447–453, April, 1961. 1 fig., 26 refs.

The authors of this paper from the University and the General Hospital, Cincinnati, Ohio, observed an " epidemic of apparent neonatal jaundice " following administration of novobiocin to control an outbreak of staphylococcal infection in a nursery for newborn infants. All infants admitted to the nursery were given 50 mg. of novobiocin 8-hourly. The incidence of neonatal icterus

significantly increased over the period of novobiocin administration, and this increase did not appear to be due to staphylococcal infection, because no overt staphylococcal disease was encountered during that time.

It is pointed out that yellow discoloration of the skin has been observed in newborn rats given single large doses of novobiocin subcutaneously. The results of the present investigation into the nature of the yellow pigment indicate that the methods used to differentiate bilirubin from the novobiocin pigment are not reliable. The pigment giving a positive van den Bergh reaction has the same chromotographic characteristics as bilirubin, whether it is obtained from serum of infants treated with novobiocin or from infants with icterus due to other causes. Excessive haemolysis as the cause of the hyperbilirubinaemia could not be proved by the gross methods used, but neither was it excluded. There was no morphologically recognizable evidence of hepatic damage by novobiocin in rats and rabbits injected with the drug.

The finding that novobiocin decreased hepatic bilirubin clearance in adult rabbits is, in the authors' view, further evidence for interference with bilirubin excretion and explains " the startling incidence of yellow babies when novobiocin was administered... Presumably novobiocin could interfere with bilirubin metabolism by enzymatic blockade... but the manner by which this occurs is unknown ". *Marianna Clark*

1041. **Toxicity of Drugs in the Neonatal Period.** [Review Article]
W. L. NYHAN. *Journal of Pediatrics* [*J. Pediat.*] **59**, 1–20, July, 1961. 6 figs., bibliography.

1042. **Auscultation of the Heart—Early Neonatal Period**
M. BRAUDO and R. D. ROWE. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **101**, 575–586, May, 1961. 13 figs., 21 refs.

The heart sounds of 80 normal full-term newborn infants were studied at the Hospital for Sick Children, Toronto, and an attempt was made to interpret the findings in the light of the physiological changes which occur at this stage of life. The first heart sound tended to be loud at birth and to decrease in intensity during the first 48 hours of life; two components of the first sound could be detected by auscultation or by phonocardiography. Splitting of the second heart sound developed within a few hours of birth at the time when the intensity of the second sound decreased; splitting was wide in about two-thirds of the patients by 16 hours and in four-fifths by 48 hours. A third or fourth heart sound was not heard or recorded in any patient. Murmurs, probably related to changing dynamics of the circulation, were heard in 48 of the patients within 24 hours of birth and were of four types. A continuous murmur beginning shortly after the first heart sound and persisting beyond the second sound was heard in 11 (14%) of the patients: it was localized to the pulmonary area and persisted until about the third day of life. A crescendo systolic murmur was heard in 4 of the patients; this began shortly after the first sound, but ended with the second heart sound, and was best heard down the left sternal border to the fourth intercostal space during the first 8 hours of life. An ejection systolic murmur was heard in 56% [*sic*] of patients. It was best heard in the pulmonary area usually 3 hours to 6 days after birth; it started after the first heart sound, was maximum in intensity in mid-systole, and ended before the second heart sound. An early systolic murmur was heard in 3 of the patients, beginning with the first heart sound and fading half-way through systole: it was louder than other murmurs and was best heard at the lower left sternal border.

It is considered that ejection systolic murmurs originate at either the pulmonary or the aortic valve and are due to increased flow of blood across the valve or to the flow of blood into a dilated vessel beyond the valve. Continuous and crescendo murmurs are attributed to flow of blood through the patent ductus arteriosus. *R. M. Todd*

CLINICAL PAEDIATRICS

1043. **The Influence of Maternal Iron-deficiency Anaemia on the Haemoglobin of the Infant**
P. LANZKOWSKY. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **36**, 205–209, April, 1961. 37 refs.

The influence of maternal iron-deficiency anaemia on the pathogenesis of iron-deficiency anaemia in infancy, which is common in Cape Town, was studied in 59 mothers and their infants selected at random from patients attending various maternity institutions attached to the University of that city. Of the 59 mothers, 33 were anaemic with a mean corpuscular haemoglobin concentration (M.C.H.C.) of 27% or less and 26 were not anaemic with an M.C.H.C. of 31% or more, these differences being highly significant. In the first 24 hours of life there was no significant difference between the infants of anaemic mothers and those non-anaemic mothers in respect of mean haemoglobin concentration, irrespective of race or the method of tying the umbilical cord. At 3 months of age 48 of the infants were re-examined and again there was no significant difference between the two groups in the haemoglobin level; the fall in this value since birth was about 8 g. per 100 ml. in all infants.

It is concluded that maternal anaemia does not lead to anaemia of the infant at birth or 3 months later when dietary and other factors have not yet influenced nutrition. *John Lorber*

1044. **Streptococcal Pneumonia and Empyema in Childhood**
S. V. KEVY and B. A. LOWE. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 738–743, April 13, 1961. 7 figs., 16 refs.

This is a review of recent experience of 11 cases of streptococcal pneumonia admitted to the Children's Hospital Medical Center, Boston, Massachusetts. In 10 of these empyema developed in spite of previous antibiotic therapy. The illness started suddenly, with chills and leucocytosis, but in other respects the clinical picture before the empyema developed resembled that of viral pneumonia. Gangrenous lesions of fingers and

toes and skin purpura occurred in one patient who had had scarlet fever a week before the onset of pneumonia. Microscopically the lesions resembled those of the Shwartzman phenomenon.

Injection of penicillin in large doses proved to be the treatment of choice. Positive cultures from nose and throat or empyema fluid were obtained in several cases after treatment with broad-spectrum antibiotics in doses recommended by the pharmaceutical manufacturer, as well as in other patients inadequately treated with penicillin. *Margaret D. Baber*

1045. **Association of Behavior Disorder with an Electroencephalographic Focus in Children without Seizures**
J. B. GREEN. *Neurology* [*Neurology (Minneap.)*] **11**, 337–344, April, 1961. 10 figs., 5 refs.

In a study of 130 children with various types of abnormal behaviour or suspected mental retardation referred to the Neurology Clinic of the U.S. Naval Hospital, San Diego, California, the author found 10 whose electroencephalogram (EEG) showed features characteristic of the interictal epileptic state but who had had no epileptic seizures. Clinically the children could be subdivided into three groups as follows: (1) 5 children showing abnormal behaviour and probable intellectual deficit whose EEGs showed temporal or occipital biphasic spikes. Anticonvulsant drugs were of no benefit except in one case in which the child became more tractable. One of these children developed a grand-mal seizure when "dilantin" (phenytoin sodium) was suddenly withdrawn after 12 months. Group 2 comprised 3 children of normal intelligence; in one of these, a girl aged 8 referred because of enuresis, the EEG showed bilateral spike abnormalities, more marked on the right than on the left; this child responded well to "mysoline" (primidone). Of the other 2 children, who were aggressive, one whose EEG showed a right temporal spike focus did not respond to anticonvulsant treatment, but the other, with generalized spike and 3-c.p.s. wave abnormality in the EEG, responded well to dilantin. The 2 children in Group 3, a girl aged 9 and a boy aged 6, suffered from paroxysmal headaches with irritability. The EEG of the girl showed a left occipital abnormality and that of the boy a left temporal spike focus. Both responded well to anticonvulsants and it is suggested that the headaches may well have represented epileptic equivalents.

The possibility that the abnormalities of behaviour in these children represented a pre-ictal syndrome is discussed. The response to anticonvulsant drugs was disappointing except in the 2 patients in Group 3.
H. S. Schutta

1046. **Brain Abscess in Congenital Heart Disease**
D. D. MATSON and M. SALAM. *Pediatrics* [*Pediatrics*] **27**, 772–789, May, 1961. 9 figs., 34 refs.

Attention is drawn to the high incidence of lesions of the central nervous system in cases of congenital heart disease, especially in the presence of cyanosis. Cohen (*Neurology*, 1960, **10**, 452) reported abnormalities in 40 out of 100 patients who died from congenital heart disease without operation. Newton (*Quart. J. Med.*, 1956, **25**, 201; *Abstr. Wld Med.*, 1956, **20**, 361) concluded that the incidence of cerebral abscess in congenital heart disease was about 4 to 6% but according to Banker (*Trans. Amer. neurol. Ass.*, 1959, **84**, 38) the incidence of occlusive vascular diseases is even higher, about 10%.

The authors describe 13 cases of cerebral abscess in association with congenital heart disease seen at the Children's Medical Center and Peter Bent Brigham Hospitals, Boston, between 1946 and 1959. When cases of cerebral abscess due to direct contamination and extension were excluded these represented one-third of all cases of cerebral abscess seen by the authors during that time. The patients (8 male and 5 female, aged 2½ to 21 years) had cyanotic congenital heart disease (Fallot's tetralogy in 9 and probable Eisenmenger's complex in one; in 3 the type of cardiac anomaly was not clear). The illness was of short duration, average 8 days (range one day to 4 weeks). The most frequent signs and symptoms could be classified in three main groups as follows: (1) signs of increased intracranial pressure—impaired consciousness in 10, vomiting in 11, papilloedema in 11 (unilateral and on the side of the lesion in 3), headaches in 8, and behaviour disorders in 4; (2) focal neurological signs—either hemiparesis or cranial nerve palsy in 10, convulsions in 8 (focal in 6), aphasia in 2, and hemianopia in one; (3) signs of infection—leucocytosis in 9, fever in 8, and meningitis in 4. The authors state that clinical evidence of septicaemia was lacking and all blood and spinal fluid cultures were sterile; there was no case of bacterial endocarditis.

The most valuable single laboratory aid to diagnosis was electroencephalography (EEG), which showed focal high-voltage slow waves over the abscess area as distinct from the findings in thrombosis where slight hemispheric slowing may occur. The cerebrospinal fluid was usually under increased pressure, with the protein content at the upper level of normal; the cell count was raised in 8 cases. Radiographs of the skull in 2 cases showed separation of the cranial sutures. The authors do not consider that angiography is justified in a condition in which the cerebral circulation is already slowed and anoxic damage likely to be present. The abscess was located by air encephalography in 3 cases. It is recommended that aspiration of the abscess should be undertaken as an emergency procedure. Thorium dioxide inserted into the cavity is then of value in following the resolution of the lesion. If the abscess cavity is well encapsulated and superficial total excision should be attempted later. The authors emphasize the importance in treatment of early diagnosis. Although 6 of the 13 patients died, only one of those subjected to elective operation did so.

[One of the valuable points of this paper is the differentiation between cerebral thrombosis and abscess. The authors point out the very great rarity of abscess under the age of 2 years, the less dramatic onset of abscess as opposed to thrombosis, and the significance of the different EEG tracings. Bacterial endocarditis does not precede cerebral abscess in congenital heart disease, a simple bacteriaemia settling on the already damaged brain being sufficient.] *H. G. Farquhar*

Public Health

1047. **Marriage and Mortality**
M. C. SHEPS. *American Journal of Public Health* [*Amer. J. publ. Hlth*] **51**, 547–555, April, 1961. 22 refs.

The average annual death rates in 1949–51 from all causes in the U.S.A. are tabulated for 9 age groups, for each sex and race (white and non-white), and for 4 marital groups (married, single, widowed, and divorced). The married group had the lowest death rates in every race-sex-age group over the age of 20 years. The widowed group had the highest rates in every race-sex-age group under 45 except for white males aged 35 to 44. In each of the marital groups the rates increased fairly steadily, after age 20, with increasing age. Various explanations have been offered for the relatively lower rates experienced by married persons as shown by these and other data. It has been suggested that healthy persons are more likely to marry than others, so that the married group is pre-selected for a favourable mortality experience. In addition, errors in classification by marital state in both census of population and death registration data have been thought to contribute to the marital differences in mortality. The observed excess mortality in young widowed persons has been the subject of particular attention.

In this report the death rates are based on denominators derived from a sample of about 20% of the population in 1950. The sample was planned to include 1 in 5 of the population, but the plan was not completely followed and a slightly higher ratio of females than of males over 25 was included; no attempt was made to overcome this bias in estimating the total population in each sex group. A table shows that differential errors were also likely in the sex-marital groups, but whether or not they were relatively similar in all race-age subgroups is not known. There is some evidence in a table showing the age distribution estimated from the sample of widowed and divorced persons that some subgroups had relatively large errors compared with others. Errors in statements about marital condition at death registration cannot be checked easily, but it is pointed out that motor vehicle and other accidents featured as a large cause of death in groups where the widowed mortality was higher than the married. Subsequent death of both marriage partners who sustain a fatal injury might, and theoretically should, result in the first to die being classified as married and the second as widowed.

A table shows for each race-sex-age group, as before, the ratios of the mortality of single, widowed, and divorced to that of the married. The author criticizes the use of such ratios and has elsewhere suggested another method of assessing the " increased risk of death " experienced by the unmarried groups. This method is briefly explained and is used to tabulate indices of absolute risk in each unmarried group for the race-sex-age groups. The rank order of the three marital groups with this index is consistent with that for the mortality ratios and the original rates. The new index, however, emphasizes the adverse experience of males and non-white groups, but, more important, suggests higher and increasing risks at the older ages for unmarried groups than is apparent from the mortality ratios.

E. A. Cheeseman

1048. **The Effect of Different Types of Cooking on Artificially Infected Meat**
P. K. SYLVESTER and J. GREEN. *Medical Officer* [*Med. Offr*] **105**, 231–235, April 21, 1961. 5 figs., 3 refs.

To reduce the risks of food poisoning in communal feeding, public health authorities advise against cooking meat before the day when it is to be eaten. There are, however, obvious administrative advantages in cooking meat slowly overnight and having it ready by mid-morning for that day's lunch, and the authors of this paper, at the request of Reading School Meals Service have carried out experiments to compare the effectiveness of orthodox (same day) and of overnight cooking of meat for the destruction of the organisms of food poisoning. Separate pieces of blotting-paper were soaked with cultures of test strains of *Staphylococcus pyogenes*, *Salmonella typhimurium*, and a readily sporing, heat-resistant *Clostridium welchii* and inserted into the central and peripheral parts of meat joints weighing 4 to 5 lb. (1·8 to 2·26 kg.) each; thermocouples were placed at suitable points either in or on the meat and connected to a multipoint temperature recorder. Some of the meat was roasted overnight in a gas oven at " regulo " setting ¼ maintained for 16½ hours; a temperature of 150° F. (65·5° C.) inside the meat was attained in 6½ to 9 hours. The more orthodox roasting was found to produce a temperature of 150° F. (65·5 C.) inside the meat within some 3 hours, rising by a further 5° to 10° F. (2·8° to 5·5° C.) in the remaining half-hour of cooking. Overnight cooking was found to be as effective as the more orthodox method in destroying heavy infections with the *Staphylococcus* and *Salmonella* test strains, but *Cl. welchii* survived both the cooking processes—slow overnight treatment to a greater extent than orthodox. In experiments with stewing steak it was found that a temperature of 170° F. (76·65° C.) was attained in about 2 hours and maintained thereafter. None of the test organisms inoculated were recovered from the steak.

Investigations on a large number of samples of raw meat from establishments under contract to the School Meals Service have shown 28% to be infected with *Cl. welchii*, but this organism was not found in any of 16 samples of gravy made in 2 of the school-meal kitchens from the juice of meat stewed overnight and subsequently consumed by school-children without any untoward result.

J. Cauchi

1049. **The Incidence of Heat-resistant *Clostridium welchi* in Some Raw Meat Supplies**
P. K. Sylvester and J. Green. *Medical Officer* [*Med. Offr*] **105**, 289–290, May 19, 1961. 2 refs.

The authors have reported [see Abstract 1048] experimental findings on the efficacy of different ways of cooking meat which had been first infected with food poisoning organisms, including *Clostridium welchii*. In the present paper they describe a search in raw meat for infection with the heat-resistant spores of *Cl. welchii*. Between January and July, 1960, they examined 713 samples of raw meat from 405 carcases. The meat from 319 of the carcases was taken from butchers' establishments which were under contract to provide meat to the Schools Meals Service. The remaining 86 carcases were sampled at the abattoir in the first three weeks of July, soon after the animals had been killed, 56 samples being taken from the neck where the animal had been stuck for slaughtering. The samples were of beef, pork, and mutton, both English and imported. They were steamed at the laboratory before being cultured to kill all vegetative and other forms of bacteria which were not heat-resistant. *Cl. welchii* were isolated from 91 (28%) of the 319 carcases sampled at the butchers' and from 19 (22%) of the 86 sampled at the abattoir. The infection was more often found on the exposed surface than within the tissue substance, and the authors discuss the possibility of infection being spread over the meat in the course of handling. *J. Cauchi*

EPIDEMIOLOGY AND IMMUNIZATION

1050. **Virus Excretion after Mass Vaccination with Attenuated Polioviruses in Hungary**
I. Dömök, E. Molnár, and A. Jancsó. *British Medical Journal* [*Brit. med. J.*] **1**, 1410–1417, May 20, 1961. 8 figs., 22 refs.

Virus excretion after mass vaccination with attenuated polioviruses in Hungary has been investigated, 2 surveys being carried out, one in Györ-Sopron County and the other on a nation-wide basis, between November, 1959, and February, 1960. In the county survey 2 doses of trivalent vaccine were fed, and 141 children aged 9 months to 15 years were tested repeatedly for virus excretion during a period of 3 months. In the nation-wide survey the 3 Sabin strains were fed at monthly intervals, and similar tests were carried out on 226 children aged under 4 years.

The results demonstrated that, before feeding took place, enteroviruses were excreted by 32·5% and 17·2% of the children tested in the 2 surveys respectively. The excretion rate for enteroviruses attained its peak in the first week following the first feeding of the trivalent vaccine. The highest excretion rate for polioviruses was 72·5% after the first vaccination and 9·2% after refeeding and the corresponding cumulative rates were 81% and 16·2% respectively. In all the age groups tested, of the 3 virus strains, the Type-3 strain was re-isolated most frequently and the Type-1 strain least frequently. The implantation of these 2 vaccine strains was found to be delayed in children under 2 years of age—a finding which was probably attributable to some interaction between them; the trivalent vaccine Type-3 strains were isolated almost exclusively after refeeding. In the majority of the positive cases the excretion between the 2 feedings was continuous; excretion following refeeding, therefore, did not invariably indicate a new implantation. The excretion rate for Coxsackie and E.C.H.O. viruses was found to fall rapidly after the first oral vaccination. The isolation rate after separate feeding of the 3 vaccine strains was highest for the Type-3 strain and lowest for the Type-1 strain. The data from the geographical areas surveyed demonstrated a correlation between the local incidence of poliomyelitis in the previous years and the corresponding post-vaccination excretion rate of the Type-1 vaccine strain; the re-isolation rate of the Type-3 strain exceeded the level expected on the basis of the prevaccination circulation of homotypic wild strains.

It has been shown by earlier investigators that after feeding attenuated poliovirus strains, as occurs after natural asymptomatic infection, the developing immunity is not only humoral, as the intestinal tract also develops resistance against reinfection. The findings in the county survey in the present study give strong support to this view. *R. G. Meyer*

1051. **Measurement of the Protective Effect of Attenuated Poliovirus Vaccine**
J. Knowelden, J. H. Hale, P. S. Gardner, and L. H. Lee. *British Medical Journal* [*Brit. med. J.*] **1**, 1418–1420, May 20, 1961. 2 refs.

The technique which has been used successfully to assess the protective effect of such vaccines as inactivated poliovirus vaccine, whooping-cough vaccine, and B.C.G. is not readily applicable to the measurement of the effectiveness of attenuated poliovirus vaccines. In an attempt to solve this problem, therefore, the authors have reanalysed the data recorded during the Type-1 epidemic in Singapore in late 1958 and early 1959. In this period Sabin Type-2 vaccine was fed to approximately 200,000 of the half-million children under 10 years of age, beginning in the 12th week of the epidemic. In each subsequent week estimates were made of the child populations, the children being placed in 3 categories: (*a*) those unvaccinated; (*b*) those vaccinated less than 8 days previously; and (*c*) those vaccinated 8 or more days previously. The results demonstrated that while the number of patients (8) who developed paralytic poliomyelitis less than 8 days after vaccination was near that expected at the rates in unvaccinated children (10·02), the 5 cases observed in children vaccinated a longer period before onset were many fewer than the number expected, 39·46.

The authors conclude that a week after feeding the Sabin Type-2 strain there was, as a result of the vaccination, a substantial reduction in the risk of paralytic disease. It has been observed, however, " that one of the difficulties in interpreting such a pattern is the uncertainty whether vaccinated children were in some way selected and naturally subject to lower rates even without prophylaxis. The experience of children vaccinated less than 8 days before onset suggests that such selection

was not taking place". The data indicate that "the vaccinated children were not subject to such a reduced natural liability to infection as could explain their favourable experience after 8 days from feeding".

R. G. Meyer

1052. **Poliomyelitis Vaccination with Live Poliovirus**
F. BUSER and M. SCHAR. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **101**, 568–574, May, 1961. 7 figs., 17 refs.

This study of vaccination with live poliovirus from the Federal Office of the Swiss Public Health Department, Berne, was intended to obtain the following information. (1) "The immunogenic properties of the live avirulent polio vaccine. (2) The rate of intestinal infection and the duration of virus excretion. (3) The spread of the vaccine virus from vaccinated persons to nonimmune contacts. (4) The genetic stability of the virus strains used." Koprowski vaccine (CHAT Type 1 and Fox Type 3) was used. Altogether, 256 persons aged 0 month to over 20 years received Type-1 vaccine. Of 123 triple-negative infants and children up to 10 years, 99% excreted virus after 10 days, 58% after 30 days, and none after 120 days. Among 212 infants and children up to 10 years, 74% of all previously Type-1 negative children reached antibody titres of 1:200 and above. Among 34 infants and children who had been immunized with Salk vaccine there was "no apparent influence of the Salk vaccination on the rate of intestinal infection and antibody formation following live virus vaccine ingestion". In more than one-third of 39 adults with no detectable pre-existing Type-1 antibodies excretion of virus could not be detected on the 10th day after vaccination, although in most cases there was a significant rise in antibody level. A study of the spread of Type-1 virus in 50 families showed contact infection in 19 children (25%) and in 16 families (32%). No alteration in the neuro-virulence of virus recovered from contact-infected children was found. Investigation of the sera of 20 infants 2 years after vaccination showed practically unchanged titre values. Type-3 vaccine was given to 90 persons who had had Type-1 vaccine 1 to 12 months before. Of 67 Type-3 negative persons, 91% excreted virus on the 10th day and 57% on the 30th day. Of 68 persons previously negative for Type 3, 95·5% gave significant antibody responses. Spread of virus was found in only one out of 12 families. Of 20 infants tested after 18 months, an excellent persistence of antibody was found in 16. In 50% of cases a heterologous Type-2 antibody response occurred which showed a significant fall in titre after one year.

There was no reported poliomyelitis in Berne during the period of the observations and for 2 months thereafter, which emphasizes the reliability of these results. The authors also remark that neither passive immunity nor Salk vaccination affected any of the observations as they were much the same as for those who did not have this protection.

[This investigation again confirms the superior quality of oral immunization, while at the same time emphasizing the problems to be considered in carrying out this form of immunization.] *Kurt Schwarz*

1053. **Influenza Vaccination in Children**
J. J. QUILLIGAN JR., P. F. SALGADO, and B. ALENA. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **101**, 593–601, May, 1961. 37 refs.

After the epidemic of Asian influenza in 1957 a number of mentally retarded children aged 2 to 12 years in an institution were selected for immunization with Asian influenza vaccine. The purpose of the present report from the Los Angeles County Hospital, California is: "to show the protective effect of the influenza vaccination during the course of the epidemic [of 1959–60]; to relate the simultaneous adenovirus and herpes simplex infections; and to show that good protection of children against influenza requires repeated doses of vaccine". In the first epidemic, which occurred 6 weeks before the first dose of the vaccine was given, the crude attack rate among the 3,300 patients of the institution was 72%. Thus for most of the children the vaccination represented their second exposure to the A2 type of virus. The first dose was of a monovalent vaccine containing 400 C.C.A. units of the A Japan 305 strain of Type-2A influenza virus per ml. The next 3 doses were of polyvalent material containing 400 C.C.A. units of Type A2, 200 units of swine and Great Lakes Type B, and 100 units of the P.R.8 strain of Type A and the P.R.301 strain of Type A1 per ml. The study covered a period of 28 months during which some of the children were lost owing to leaving the institution, developing illness, or other causes. At first 176 children were given, alternately, either 0·5 ml. of vaccine subcutaneously or 0·1 ml. intracutaneously. The subsequent doses of polyvalent vaccine were given in the same dosage and manner after intervals of 3, 4, and 15 months respectively, but only 113 children received all 4 doses. Between 25 and 27 unvaccinated children acted as controls for serological tests. Febrile reactions occurred in 25% of cases with 0·5 ml. and 11% with 0·1 ml. The antibody response to the 0·5-ml. dose was twice as great as that to 0·1 ml. (This was true of all types except Great Lakes Type B, of which 0·1 ml. gave a better response.) Strain P.R.301 gave the maximum response after the first dose, while the others gave a better response with each succeeding dose.

When the 1959 epidemic occurred influenza virus Type A2 was predominant. Adenovirus (Types 2, 3, and 5) and herpes simplex had occurred throughout the observation period in an endemic fashion. When comparisons were made of the incidence of clinical evidence of respiratory disease in the vaccinated and unvaccinated it was therefore assumed that all cases were of influenza. The attack rate was 13% amongst the 113 children who had had 4 doses of vaccine compared with 49% among 152 non-vaccinated children. Among other groups of children not included in the main study who had received 1, 2, or 3 doses of vaccine there was a lesser degree of protection. A suggested dosage scheme is 0·1 ml. followed 2 to 4 weeks later by 0·25 ml. and by a booster dose of 0·5 ml. 6 months later. Annual doses of 0·5 ml. may then be given to susceptible groups. [This assessment provides useful information about the action and application of influenza vaccine.] *Kurt Schwarz*

Industrial Medicine

1054. **Tomographic Appearances in Pneumoconiosis.** (L'indagine stratigrafica nelle pneumoconiosi)
C. GARAVAGLIA, C. POLVANI, and A. UBEZIO. *Medicina del lavoro* [*Med. d. Lavoro*] **52**, 98–126, Feb. [received June], 1961. 27 figs., 36 refs.

In this paper the authors first describe the Geneva (1958) classification of persistent pulmonary opacities due to the inhalation of mineral dusts and then discuss in detail the use of tomography in the diagnosis of certain stages of the classification, illustrating their arguments with cases from the archives of the Clinic of Industrial Medicine of the University of Milan. In this clinic tomography is usually unidirectional, taken in the antero-posterior projection, though tomograms in the lateral and even the oblique planes are also used at times.

For linear opacities tomography is not of much value compared with a first-class standard radiograph, though it is of great value in demonstrating the lymph-node reactions which are always present at this stage. Small opacities of Types p1 and p2 tend to be concealed in tomograms and can only really be detected when they reach the classic pin-head size. However, in the authors' experience, it is possible to demonstrate by tomography micronodulation of Type p3 that is hidden on the standard radiograph by diffuse punctiform lesions. Micronodular and miliary opacities of Type m can be located better and nodular opacities of Type n can be better differentiated from tuberculous lesions by tomography than plain radiography. With large opacities of Category A tomography can define the limits of the site precisely and indicate the opacity of any initial condensation, especially in the subclavicular area, while in Category B it can differentiate pneumoconiotic lesions from those of silico-tuberculosis or tuberculosis. The authors draw attention to an unusual form of non-pneumoconiotic calcification which seems to occur along the longitudinal axis of a silicotic mass, suggesting that the calcification is secondary to the formation of areas of condensation and probably not to the confluence of nodules.

In a further section of their paper the authors deal with the use of tomography in the sequelae and complications of pneumoconiosis, including tuberculosis, cancer, emphysema of all descriptions, and the middle-lobe syndrome, and in the post-initial stages of asbestosis. Its value in demonstrating cavities otherwise concealed by pneumoconiotic thickening and the changes in the hilar and mediastinal lymph nodes, which may undergo changes in silicosis independent of the gravity of the parenchymal process, is emphasized; this is especially the case in the egg-shell type of enlargement. Discussing their experiences and results, the authors point out that every time when reading and interpreting a series of radiographs in a case of pneumoconiosis they are struck by the polymorphism of the condition so that tomography is an almost indispensable aid. In any case considerable experience is necessary for any satisfactory interpretation, but the indications for tomography are so extensive that this is almost always necessary. They put forward a list of conditions in which the Milan clinic has found it to be of most value, starting with the differential diagnosis between pneumoconiosis, tuberculosis, and silico-tuberculosis, especially of the cavitating type. Its limits are represented mainly by the density of the films intrinsic in the method.

[A number of most interesting standard radiographs and tomograms, taken at the same time, are included for comparative purposes. The paper deserves to be read in full.] *W. K. Dunscombe*

1055. **Pulmonary Ventilatory Functions of Coalminers in Various Areas in Relation to the X-ray Category of Pneumoconiosis**
A. L. COCHRANE and I. T. T. HIGGINS. *British Journal of Preventive and Social Medicine* [*Brit. J. prev. soc. Med.*] **15**, 1–11, Jan., 1961. 3 figs., 20 refs.

The authors of this paper from Llandough Hospital, Penarth, and the Welsh National School of Medicine, Cardiff, have studied pulmonary ventilatory function in relation to the radiological category of pneumoconiosis, the material being derived from surveys previously carried out on miners in the Rhondda Fach, in Leigh, and in Staveley. Information was available concerning occupational history, the results of respiratory function tests, symptoms, and smoking habits; chest radiographs and anthropometric data were also available. For purposes of comparison use was made of two further surveys conducted in agricultural areas.

The investigation showed that in simple pneumoconiosis there was little evidence of increasing disability with increasing radiological category of the disease. The finding in some earlier surveys that miners without simple pneumoconiosis were likely to be more disabled than those with this condition was not confirmed and possible explanations are discussed. It is considered that the evidence for decreased ventilatory function in miners without pneumoconiosis is questionable.

As regards the influence of region or area on the ventilatory function of miners and ex-miners, the only significant difference between the populations was that observed between an agricultural area and the Leigh area (which is well known to have considerable atmospheric pollution). Among the mining population, a significant regional difference was observed between the Rhondda Fach and Staveley. It is suggested that this may have been attributable to coincidental bronchitis, since this condition is more prevalent in the Rhondda. It is also suggested that dust concentrations may have been about 50% higher in the Rhondda Fach than at Staveley. The number of years spent at the coal face,

the existence of regional atmospheric pollution, and the differential migration of the fitter members of the community during periods of depression and unemployment may also be factors.

The number of cases of progressive massive fibrosis in this investigation was small, but it was noted that the early stages of this condition cause very little disability and that the area of the massive shadow is the sensitive index so far as mortality is concerned.

Finally the balance of the evidence suggested, in the authors' view, that elderly miners tend to have slightly more ventilatory disability than they would have had if they had never become miners. *L. W. Hale*

1056. **Stannosis: Benign Pneumoconiosis Due to Tin Dioxide**

A. J. ROBERTSON, D. RIVERS, G. NAGELSCHMIDT, and P. DUNCUMB. *Lancet* [*Lancet*] **1**, 1089–1093, May 20, 1961. 14 figs., 19 refs.

In Britain pneumoconiosis due to tin oxide (stannosis) was probably first recorded in Liverpool, and, although working conditions have changed in the tin industry, it seems that the chief risk at present comes from the filling and emptying of bags of cassiterite concentrate and from the hot gases (probably tin dioxide) produced during reduction and smelting of the ore, whereas some years ago the transport of the ore in the factory on bogies was associated with much dust.

Out of the original 121 patients in whom the condition was discovered by chest radiography, 7 have since died and come to necropsy and these form the basis of the present study. Lungs were prepared by the Gough–Wentworth technique, the better inflated lung in each case being retained for whole section, histological examination, and x-ray-emission microanalysis, while the other was dried and used for dust identification by electron microscopy and chemical and x-ray diffraction analysis. Blocks typical of each whole lung were prepared for serial histological section and stained with standard stains and those for reticulin and collagen. The last section of the series was microincinerated.

Dust foci (varying from 2 to 5 mm. in size) consisted essentially of dense aggregates of dust-laden macrophages surrounding the respiratory bronchioles. Focal emphysema, characteristic of many cases of coal-worker's pneumoconiosis, was little in evidence, and only 2 of the 7 cases showed any histological evidence of bronchitis. A "remarkably low" reticulin response to dust-laden macrophages and a slight amount of collagen in the dust foci were discovered, in contrast to the increased content found in coal-worker's pneumoconiosis.

Portions of lung from 2 patients which were analysed after ashing contained 40% and 35% respectively of tin dioxide. The authors [rightly] did not consider this a satisfactory method of expression and therefore estimated the actual amount of tin dioxide in one lung, which proved to range from 0·5 g. to over 3·0 g. Fairly good correlation between the values for tin dioxide content of the lung and radiological category was found. With comparable categories the lungs of tin workers appear to contain about one-tenth of the amount of dust found in coal-workers with simple pneumoconiosis, but the higher atomic number of tin as opposed to carbon explains this.

It is pointed out that the dust in lung phagocytes looks very like carbon dust and is easily mistaken for it unless analysed. An electron probe was applied to phagocytes in one case and the nature of the dust easily identified.

When the chest radiographs of these cases were first seen silicosis was a possible diagnosis, although there was no "clinical evidence of this". Since the quantity of quartz found in the lungs in these cases was small (from 0 to 200 mg.) as compared with that in classic silicosis (from 2 to 4 g.) there was no pathological evidence of it either. Progressive massive fibrosis was not seen.

The authors conclude that "the striking radiological changes, the good pulmonary function, the longevity of the workmen as a whole, and the absence of any significant pathological response to the tin dust in phagocytes, would seem to justify the title '*benign* pneumoconiosis due to tin dioxide' as an alternative to 'stannosis'." *W. Raymond Parkes*

1057. **The Role of Bacterial Endotoxins in Occupational Diseases Caused by Inhaling Vegetable Dusts**

B. PERNIS, E. C. VIGLIANI, C. CAVAGNA, and M. FINULLI. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **18**, 120–129, April, 1961. 8 figs., 26 refs.

Inhalation of various vegetable dusts gives rise to occupational diseases in which the main symptoms are shortness of breath, coughing, fever, and general malaise. These symptoms are frequently prominent on Mondays or on resuming work after one or two days' interruption. Cotton dust is one of the vegetable dusts most often recognized as responsible for occupational disease. It has in the past been suggested that these diseases may be caused by the endotoxin of a Gram-negative bacterium known as *Aerobacter cloacae*. The authors of this paper from the University of Milan claim to have found the constant presence of endotoxins in cotton dust in textile mills, and they record a study of the effects of inhalation of purified endotoxin in rabbits and man. They claim that amongst workers in a pharmaceutical plant where typhoid vaccines were manufactured the inhalation of endotoxin produced in all subjects spontaneous bronchial affections, and those with a history of chronic bronchitis had to be excluded from the rooms where the typhoid vaccine was prepared because they often had asthmatic attacks, especially when centrifuging bacterial suspensions.

Moulds are among the main contaminants of many cellulose-rich materials, but there is no proof that they are the cause of the disease, and the authors state that "moist cellular-rich materials not only favour the development of moulds, but also of Gram-negative bacteria of the aerogenes-capsulatus group that are often able to ferment the polysaccharides". They suggest that byssinosis and diseases of the mill-fever group might result in a condition of immunological hypersensitivity retaining some of the aspects of the reaction to endotoxins, such as tolerance. More experimental work coupled with observations on man will be necessary to test this possibility. *Kenneth M. A. Perry*

Toxicology

1058. **Managing Salicylate Poisoning in Children: an Evaluation of Sodium Bicarbonate Therapy**
C. F. WHITTEN, N. M. KESAREE, and J. F. GOODWIN. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **101**, 178–194, Feb., 1961. 42 refs.

Writing from Wayne State University College of Medicine, Detroit, the authors point out that many poisons can be detoxicated, degraded, or removed from the body, but that salicylates cannot be detoxicated and natural degradation of the salicyl radical cannot be hastened. Treatment has hitherto included exchange transfusion or dialysis. In this study the authors investigated the effect of alkalinizing the urine, a procedure which is known to accelerate salicylate excretion, but has, mainly on theoretical grounds, been regarded as hazardous as tending to accentuate the already existing systemic alkalosis. In 20 children aged 4 months to 4 years suffering from salicylate poisoning, after gastric lavage the blood chemistry was assessed and urine obtained through an indwelling catheter. From 20 to 40 ml. of a 0·89 M solution of sodium bicarbonate was then injected quickly. Usually the urine was alkaline at the end of 10 minutes, but if not a further 15 to 20 ml. of the solution was injected. Alkalinization was maintained by continuous intravenous sodium bicarbonate in weaker solution, the procedure being controlled by frequent estimation of the blood and urine constituents. It was found that with effective alkalinization of the urine the plasma salicylate levels were halved in 2 to 5 hours. Coincidentally the protein-bound salicylate level rose, though this had a fixed ceiling at the varying salicylate concentrations. In the urine the salicylate was nearly all in the free form. On admission, many of the patients showed metabolic or respiratory alkalosis. The addition of mannitol to the infusion to produce osmotic diuresis further increased the rate of salicylate excretion, but the authors consider that this increase was not sufficient to warrant the routine use of this procedure.

All the patients recovered, but symptomatic improvement did not always keep pace with lowering of the blood salicylate level. The authors conclude that alkalinization with sodium bicarbonate produces as good results as dialysis or exchange transfusion. They agree that the production of alkalosis is a risk, though symptoms attributable to this did not appear in the present series. All the patients showed hypokalaemia, but this caused no symptoms, and hypernatraemia also occurred; the authors recognize the risk of intracellular sodium intoxication, and although no complications arose from this in the present study, they nevertheless recommend giving potassium with the sodium bicarbonate infusion. They conclude that the treatment of salicylate poisoning by alkalinization with sodium bicarbonate is both simple and safe, and in their view it is indicated in such cases even when there are no acute symptoms.

[The original should be studied by those who contemplate treating salicylate poisoning by this means.]

Gavin Thurston

1059. **Lead Encephalopathy in Children: Intravenous Use of Urea in Its Management**
J. GREENGARD, W. ROWLEY, H. ELAM, and M. PERLSTEIN. *New England Journal of Medicine* [*New Engl. J. Med.*] **264**, 1027–1030, May 18, 1961. 12 refs.

In 1959 in Chicago 142 children with lead poisoning were seen at Cook County Children's Hospital; in 120 cases this was due to eating lead-containing plaster and paint flakes, and the other 22 were cases of acute poisoning due to burning of battery casings. The majority of the children were between 18 months and 3 years old. In 42 cases a diagnosis of lead encephalopathy was made, and 10 of these patients died. Of these 42 cases, 30 received urea intravenously; on the basis of presenting symptoms these were classified as severe cases. The urea was usually given in a 4% solution in 5% dextrose in water, though in a few severe cases a 30% solution was used. The dosage was 1 g. per kg. body weight daily and the solution was given by continuous intravenous drip at a rate not exceeding 60 drops per minute. Care was taken to ensure that urinary secretion was adequate before urea administration was started, and a blood urea level above 75 mg. per 100 ml. was considered undesirable. Where indicated other measures were also employed, including the administration of sodium calciumedetate and of anticonvulsants and surgical decompression. It is pointed out that lumbar puncture can be dangerous in lead encephalopathy owing to the danger of medullary herniation through the foramen magnum; for this reason it should be carried out only with the needle connected to a manometer in a closed system. Despite this precaution such complications as respiratory arrest followed lumbar puncture in several cases.

Of the 30 children treated with urea, 5 died, and 5 of the 12 children who did not have this treatment also died. Extensive surgical decompression was carried out on 11 of the 42 children, and 5 of these died; in this group 6 had received urea in addition to surgery, with 3 recoveries. Another 24 children were treated with urea without decompression; 21 recovered and 3 died. The remaining 7 children were given neither surgery nor urea, and of these 5 recovered and 2 died. The children subjected to surgery and those who received neither surgery nor urea were the most severely affected, and some died before urea could be administered or surgery carried out. Of 15 children it was possible to follow up, 9 had some residual neurological or mental disorder.

Stress is laid on prevention and on the importance of early diagnosis. Many of the children in the series "had been seen by physicians who failed to consider lead poisoning in the somewhat vague and atypical picture presented".

P. T. Main

Anaesthetics

1060. **The Distribution of Inspired Gas during Thoracic Surgery**

J. F. NUNN. *Annals of the Royal College of Surgeons of England* [*Ann. roy. Coll. Surg. Eng.*] **28**, 223–237, April, 1961. 9 figs., 20 refs.

Previous work has suggested that serious maldistribution of respired gases may take place during thoracic surgery, particularly as in the lateral position the blood flow in the under lung is greater but the ventilation is less than it is in the upper. In this study, reported from the Royal College of Surgeons of England, London, to investigate this problem further 14 patients were investigated—6 in the lateral position, 6 prone, and 2 supine. Only one patient (lateral group) had severe emphysematous changes and 2 (supine) were cooled to 29° C. for repair of atrial septal defects. Anaesthesia was induced with a short-acting barbiturate and maintained with nitrous oxide and oxygen and a relaxant. A cuffed endotracheal tube was passed. All patients were ventilated artificially at a uniform minute volume for about 40 minutes, by which time the chest had usually been open for 15 minutes. The measurements were then made over the next 7 minutes—in the cases of atrial septal defect this was just before cardiac arrest. Anatomical dead space, arterial blood and expired gas collected for estimation of the physiological dead space, and then anatomical dead space again, were measured in that order. Ventilation, CO_2 output, and arterial pCO_2 were measured simultaneously.

The anatomical dead space (lateral and prone positions only) was about half the normal value for the conscious subject (due to the endotracheal tube), increased slightly with tidal volume, and was unaffected by position. The physiological dead space was appreciably larger than the anatomical dead space (in contrast to the conscious patient, in whom it is equal); it increased with the tidal volume, equalling about one-third the tidal volume, and was unaffected by posture. This dead space tended to be larger when the exposed lung was fully expanded, and suggested that the bulk of the physiological dead space was in this lung.

Unilateral ventilation and perfusion via a Carlen catheter was measured in 2 patients in the lateral position. In the first case, when the upper lung was fully expanded the ventilation was 5 times and the CO_2 output 3 times that of the lower lung. In the second case, when the lung was retracted so that it filled only half the pleural cavity, ventilation and CO_2 output were less than in the under lung. The difference between the arterial and end-tidal pCO_2 was a mean of 7 mm. Hg, but was 23 mm. Hg in the emphysematous patient. The mean CO_2 output was 14% whether the patient was lateral or prone, but was 40% below basal value in the 2 hypothermic patients. The over-all efficiency of ventilation as measured by arterial pCO_2 was normal except in the emphysematous patient, suggesting that the open chest does not require increased ventilation. In the hypothermic patients hyperventilation readily occurred (arterial pCO_2 14 and 10 mm. Hg respectively) and the mean physiological dead space was 18% of the tidal volume.

In every case maldistribution occurred, while the exposed lung was preferentially ventilated unless it was retracted. Although maldistribution tended to raise the arterial pCO_2, the use of an endotracheal tube and the lowering of CO_2 output in the anaesthetized subject tended to counteract this effect. It appears, therefore, that normal minute volumes of ventilation could maintain a normal pCO_2. It must be stressed, however, that this holds only for relatively normal lung.

D. D. C. Howat

1061. **Respiratory Complications Associated with the Use of Muscle Relaxants in Young Infants**

E. SALANITRE and H. RACKOW. *Anesthesiology* [*Anesthesiology*] **22**, 194–198, March–April, 1961. 16 refs.

Following reports that the response of newborn and young infants to muscle relaxants may differ from that of adults, the authors have conducted a study at the College of Physicians and Surgeons, Columbia University, and the Presbyterian and Babies' Hospitals, New York, designed to establish whether there is clinical support for such a view and whether any difference that might exist could be related to age, duration of anaesthesia, or change in body temperature. For this purpose they reviewed the cases of 220 infants aged under 13 weeks who had undergone various surgical procedures during a 2-year period. These fell into 2 groups: (1) 114 who did not receive a muscle relaxant during anaesthesia; and (2) 106 who were given succinylcholine (5 to 50 mg. intravenously or 15 to 65 mg. intramuscularly) and/or D-tubocurarine (0·25 to 4·5 mg. intravenously). Evidence was sought of any ventilatory inadequacy considered on clinical grounds to require assistance of respiration, and for purposes of comparison the infants were divided into 4 age groups: 0 to 7 days, 1 to 4 weeks, 5 to 8 weeks, and 9 to 12 weeks.

Respiratory complications were noted in 14 (12%) of the 114 infants who did not receive relaxants and in 29 (27%) of the 106 who did, the incidence being highest in those aged 0 to 7 days in both groups. The immediate postoperative rectal temperature was measured in 168 infants; in 82 (49%) of them it was less than 96° F. (35·6° C.), and 29 (35%) of these hypothermic infants had respiratory insufficiency. Only 10 (12%) of the 86 infants with temperatures above 96° F. (35·6° C.) developed respiratory insufficiency. Hypothermia occurred in 61% of infants who received relaxants and 37% of those who did not; 48% of the former and 16% of the latter developed respiratory insufficiency—a statistically significant difference. Among the "normothermic" patients respiratory insufficiency developed in 9% of those given relaxants and 13% of those not given relaxants. Anaesthesia of more than 2 hours' duration

had a complication rate of 32% compared with 16·5% for anaesthesia of less than 2 hours, a finding which is considered to be of borderline significance.

The authors discuss these findings on the basis of (*a*) the presence of a myasthenic-like state (Stead, *Brit. J. Anaesth.*, 1955, **27**, 124); (*b*) simple overdose; and (*c*) the combined effect of neuromuscular block with hypothermia. Neither hypersensitivity nor a myasthenic-like state could be excluded, though some infants responded normally to D-tubocurarine. It was difficult to relate postoperative respiratory complications to simple overdose. However, the findings suggest that the use of relaxants may produce postoperative respiratory difficulties in young infants, not only because of the ease of overdosage, but also because of the tendency for the normal fall in body temperature under anaesthesia to increase. Whether relaxants had been given or not, the main fall in temperature occurred during the first 2 hours, but whereas in the "non-relaxant" group the temperature then remained stable, in the "relaxant" group it continued to fall further. *Raymond Vale*

1062. **Alterations in Response to Somatic Pain with Anaesthesia. VI: The Effect on a Non-barbiturate Intravenous Anaesthetic—G.29505**

J. W. DUNDEE and R. C. HAMILTON. *British Journal of Anaesthesia* [*Brit. J. Anaesth.*] **33**, 230–234, May, 1961.

Analgesimetry studies have been carried out on a new non-barbiturate intravenous anaesthetic—G.29505 (2-methoxyl-4-allylphenoxyacetic acid-N:N-diethylamide). The method employed consisted of the application of graded pressure to the anterior surface of the tibia. In contradistinction to the action of thiopentone, subhypnotic doses of G.29505 decrease the sensitivity to somatic pain. This effect was very transient. During the recovery period after larger doses of the drug, there was a gradual return of readings to normal but at no time was an anti-analgesic action detected. Even with large doses, the duration of this analgesic effect was very short.

The clinical significance of these findings has been discussed and in this, or related compounds, an intravenous anaesthetic may be found which can be used safely for short procedures without supplementary nitrous oxide and oxygen.—[Authors' summary.]

1063. **Barbiturate Antagonists: a Critical Study**

E. F. O'RIORDAN and P. S. MARCUS. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **40**, 188–198, March–April, 1961. 10 figs., 14 refs.

This investigation of barbiturate antagonists was carried out at Boston City Hospital on patients undergoing relatively minor surgery on the lower half of the body under spinal anaesthesia. Premedication was with 50 to 100 mg. of "nembutal" (pentobarbitone sodium) and 0·4 mg. of atropine. After the induction of spinal anaesthesia the blood pressure, pulse rate, and rate and depth of respiration were noted and thiopentone in 2% solution then given intravenously until the patient was in a light plane of anaesthesia, which was maintained with an intravenous drip of 0·2% thiopentone. Meanwhile the blood pressure, pulse, and respiration were recorded every 5 minutes until a steady plane of anaesthesia (as confirmed by the electroencephalogram) was achieved. At this point a blood sample was withdrawn for determination of the thiopentone level and the circulatory and respiratory response to 5% CO_2 was also tested. The particular barbiturate antagonist under study was then administered intravenously and 5 minutes later the pulse, blood pressure, respiration, and blood thiopentone concentration were again measured. Finally the response to administration of 5% CO_2 for 10 minutes was also again tested.

It was shown that bemegride (100 mg.) produced marked arousal and increased the sensitivity of the respiratory centre; no circulatory changes were noted. Methylphenidate (50 mg.) also produced excellent arousal, but failed to increase the sensitivity of the respiratory centre. The authors found that a combination of methylphenidate (50 mg. intravenously) and nikethamide (given as a continuous drip of a solution containing 50 ml. of 25% nikethamide in 450 ml. of 5% dextrose in water) produced excellent arousal and increased sensitivity of the respiratory centre which was superior to that of the other agents studied.

Mark Swerdlow

1064. **Blood Oxygen Saturation during Anaesthesia with Volatile Agents Vaporized in Room Air**

P. V. COLE and J. PARKHOUSE. *British Journal of Anaesthesia* [*Brit. J. Anaesth.*] **33**, 265–273, May, 1961. 12 refs.

An "Atlas oximeter" was used to measure arterial oxygen saturation in 105 patients anaesthetized by means of volatile agents vaporized in room air. Measurements were made pre-operatively, during surgery, and sometimes in the postoperative period. During controlled ventilation, providing oxygen was administered prior to intubation and extubation, arterial oxygen saturations compared favourably with the normal for the patient. During spontaneous ventilation, arterial oxygen saturation remained satisfactory in the great majority of cases unless marked respiratory depression occurred. When respiratory depressants such as halothane are used the anaesthetist should be prepared to assist the respiration or use additional oxygen. Arterial oxygen saturations measured during the early postoperative period were lower than those recorded during surgery.—[Authors' summary.]

1065. **The Effect of Fluothane on Myocardial Contractile Force in Man**

R. D. BLOODWELL, R. C. BROWN, G. R. CHRISTENSON, L. I. GOLDBERG, and A. G. MORROW. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **40**, 352–361, May–June, 1961. 3 figs., 18 refs.

The effects of "fluothane" [halothane] inhalation on myocardial contractile force and arterial blood pressure were studied in 17 patients in the course of operations for congenital or acquired heart disease. Contractile force was measured by means of a Walton–Brodie strain gauge arch sutured to the surface of the right ventricle. In 15 of the 17 patients depression of contractile force was observed when fluothane was administered and the

degree of depression was related to the concentration of the agent. A fall in arterial blood pressure ordinarily reflected the cardiac effects of the agent but the blood pressure often returned to normal levels during continued administration when myocardial depression persisted.—[Authors' summary.]

1066. **The Comparative and Additive Effects of Methylphenidate and Bemegride**

A. S. GALE. *Anesthesiology* [*Anesthesiology*] **22**, 210–214, March–April, 1961. 9 refs.

The author, at Mount Sinai Hospital, Cleveland, Ohio, has investigated the use in drug-induced depression of ethylmethylglutarimide (bemegride), which may produce convulsions, and methylphenidate (" ritalin "), which is effective in smaller and non-convulsive doses. The drugs were given after administration of a standard anaesthetic sequence of thiopentone and nitrous oxide–oxygen to patients undergoing uterine dilatation and curettage. Recovery times were measured to 4 end-points: (1) ability to open her eyes on command; (2) ability to repeat her name; (3) ability to give her address; and (4) ability to identify tactile stimuli. Bemegride alone in doses of 0·05, 0·1, 0·2, and 0·4 mg. per lb. (0·11, 0·22, 0·44, and 0·88 mg. per kg.) body weight was given to 100 patients, and ritalin alone in doses of 0·05, 0·1, 0·2 (optimum dose), and over 0·4 mg. per lb. (0·11, 0·22, 0·44, and 0·88 mg. per kg.) body weight to 221 patients; both drugs were given in varied dosage and sequence to 226 patients.

Bemegride alone in a dosage up to 0·2 mg. per lb. (0·44 mg. per kg.) was as effective in shortening recovery times as similar doses of ritalin alone, though the largest dose of bemegride (0·4 mg. per lb.; 0·88 mg. per kg.) was more effective than the smaller doses. Administration of ritalin, 0·05 mg. per lb. (0·11 mg. per kg.), after bemegride, 0·4 mg. per lb. (0·88 mg. per kg.), shortened recovery time considerably, as did ritalin in a dose of 0·1 to 0·2 mg. per lb. (0·22 to 0·44 mg. per kg.). Larger doses of ritalin not only failed to shorten the bemegride recovery times, but prolonged them. Ritalin proved to have a protective effect; thus administration of higher doses of bemegride (0·4 and 0·8 mg. per lb.; 0·88 and 1·76 mg. per kg.) after ritalin, 0·2 mg. per lb. (0·44 mg. per kg.), gave the shortest recovery times of all. The shortening of recovery times when both drugs were given was statistically significant. Visible tremors of the jaw or extremities occurred in 13 of the 100 patients receiving bemegride alone, but in only one of the 226 receiving both drugs, this difference being highly significant.

A number of patients with barbiturate intoxication producing deep coma were successfully treated with combinations of the two drugs. Where blood pressure had to be maintained with infusion of " levophed " (noradrenaline) the infusion could be slowed after the ritalin was given. One patient deeply unconscious after ingesting 20 g. of meprobamate responded well to the combined treatment.

The author concludes that ritalin has an additive analeptic effect to bemegride and reduces the liability to tremors and convulsions. *Raymond Vale*

1067. **" Xylocaine " for the Relief of Postoperative Pain**

E. E. BARTLETT and O. HUTASERANI. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **40**, 296–304, May–June, 1961. 3 figs., 14 refs.

After briefly discussing the pharmacology of lignocaine the authors describe a clinical trial of this drug at New England Hospital, Boston. Of 604 patients undergoing a variety of operations, half received an intravenous infusion of one litre of fluid containing 1,500 mg. of lignocaine, while the remainder served as controls. The lignocaine was given during the operation, and pain was evaluated during the first three postoperative days. Four degrees of pain were recognized and in addition the number and dosage of narcotic agents were noted.

It was found that 70% of the patients receiving lignocaine had no pain or only slight pain on the first postoperative day, as against 11% in the control group. Pain decreased progressively in both groups on the second and third days. On the third day 94% of the lignocaine-treated patients had little or no pain compared with 34% of the controls. It was also found that intramuscular administration of 200 to 500 mg. of lignocaine at the end of the operation in addition to the intravenous infusion increased the percentage of patients who were free from pain on the first day. The number of doses of narcotic required was less in the lignocaine-treated patients than in the controls. *Mark Swerdlow*

1068. **Anaesthetic and Postoperative Hazards in Rheumatoid Arthritis**

D. L. GARDNER and F. HOLMES. *British Journal of Anaesthesia* [*Brit. J. Anaesth.*] **33**, 258–264, May, 1961. 3 figs., 17 refs.

In 5 patients with rheumatoid disease respiratory difficulty during anaesthesia or unexpected postoperative death occurred. It is emphasized that such patients may be difficult subjects for the induction of anaesthesia on account of arthritis and ankylosis of the small joints of the larynx, of the cervical spine and of the temporomandibular joints. In the same way the maintenance of adequate respiratory excursions during anaesthesia may be impeded by ankylosis of the costovertebral joints. Because of these manifestations of rheumatoid disease grave respiratory complications may be precipitated in the postoperative period. Following operation, the occurrence of interstitial pneumonia in rheumatoid arthritis may delay recovery. Particularly careful and continuous observation of these patients is necessary.

In other cases with rheumatoid arthritis apparently straightforward operative procedures are followed by unexpected death. The high incidence of severe amyloidosis may determine a poor response to anaesthetic and analgesic drugs and in part account for these fatalities. Further, it is becoming increasingly evident that unsuspected and potentially dangerous infection may remain latent in joints which are the sites of rheumatoid arthritis. There is reason to suppose that such patients have an altered response to infections to which, in spite of their characteristically hyperplastic reticulo-endothelial systems, they exhibit abnormally low resistance. —[Authors' summary.]

Radiology

1069. **The Diagnostic Value of Lymphangiography**
L. JACKSON, S. WALLACE, B. SCHAFFER, J. GOULD, S. KRAMER, and A. J. WEISS. *Annals of Internal Medicine* [*Ann. intern. Med.*] **54**, 870–882, May, 1961. 7 figs., 10 refs.

Lymphangiography may be carried out by the injection of contrast material into the soft tissues, the lymphatic vessels, or the peripheral nodes. The technique of injection into the vessels, which was devised by Kinmonth in 1952 (*Clin. Sci.*, **11**, 13; *Abstr. Wld Med.*, 1952, **12**, 338) has been further developed by the authors at Jefferson Medical College Hospital and the Philadelphia General Hospital, Philadelphia (*Radiology*, 1961, **76**, 179).

Briefly, the authors' technique involves the injection of 0·25 ml. of 0·5% Evans (azovan) blue dye mixed with an equal amount of 1% procaine into the interdigital web space between the first and second toes. After about 15 to 30 minutes the lymphatic will be visible and after a skin incision has been made a suitable vessel may be entered with a 25- to 30-gauge needle, secured by a ligature, and 10 ml. of "ethiodol" iodized oil injected slowly by a manually operated apparatus at the rate of 7 ml. per hour. After injecting one lymphatic in each foot the lymph vessels and nodes of the complete lymphatic pathway to the root of the neck can be demonstrated. The vessels are best seen on a radiograph taken immediately after the injection and the nodes 24 hours later. Injection of the hand enables the axillary and supraclavicular lymph nodes to be visualized.

The authors have now studied 140 patients by this method and a number of patterns are described. The normal and inflamed lymph nodes present a homogeneous reticular pattern, metastatic carcinoma produces a "moth-eaten" appearance, and reticulo-endotheliosis results in a lacy, diffusely infiltrative pattern.

D. E. Fletcher

1070. **Problems in the Radiographic Diagnosis of Mitral Lesions, with Recent Results.** (Probleme und neuere Ergebnisse in der Röntgendiagnostik der Mitralfehler)
P. THURN. *Radiologe* [*Radiologe*] **1**, 2–18, April, 1961. 15 figs., bibliography.

In pure mitral stenosis the finding on the postero-anterior radiograph is frequently that of enlargement of the right ventricle alone. Enlargement of the left auricle can be demonstrated best in the lateral film with the aid of barium, or alternatively in the right oblique view. To assess the size of the four chambers of the heart the aid of cardioangiography is now available. The right auricle may be found to be enlarged if there is relative incompetence of the tricuspid valve.

In this paper from the University Medical Clinic, Bonn, the author attaches great importance to the finding of a clear space in the lateral film between the posterior border of the heart and the diaphragm, with a clearly visible inferior vena cava. Obliteration of this space is regarded as a definite sign of an enlarged left ventricle, with the qualification that sometimes enlargement of the right ventricle may produce indirectly a similar appearance. But generally the enlargement of the right ventricle can be assessed from the lateral film by taking into account its extent alongside the anterior chest wall. Surgeons find calcification in the mitral valve in about 30 to 40% of all cases of mitral lesions. The search for calcified mitral valves is thus of great practical importance, and it is generally agreed that the use of image-intensifiers helps greatly the demonstration of these calcifications. The author is convinced that in all cases such calcifications if present can be radiologically demonstrated, although according to previous reports this has not been achieved hitherto. In his opinion the presence of mitral calcification makes a diagnosis of pure mitral stenosis improbable, and if there remains any doubt as to whether there is also combined incompetence selective left cardioangiography is required. That calcification of the mitral valve renders the prognosis after operation more doubtful is generally acknowledged in view of the known increased occurrence of postoperative mitral incompetence. Furthermore, it is known that extensive calcification may frequently make operation technically impossible.

Venous angiocardiography helps to differentiate the size of each ventricle and also reveals any changes in volume and form of the left atrium; particular attention should be paid to the shape of the interventricular septum. Selective left angiography is often decisive and shows in cases of pure mitral stenosis a typical downward ballooning of the left atrium. In mitral incompetence the reflux from the left ventricle to the atrium can be demonstrated. Cardioangiography should always be combined with electrocardiography since naturally disturbances of rhythm must influence the findings. Left-sided angiography is of particular help when there is also combined abnormality of the aortic valves. The results of operation can be assessed by similar procedures.

F. M. Abeles

1071. **Roentgen Evaluation of Pulmonary Arterial Pressure in Mitral Stenosis**
P. M. JOHNSON, E. H. WOOD, B. S. PASTERNACK, and M. A. JONES. *Radiology* [*Radiology*] **76**, 541–547, April, 1961. 4 figs., 19 refs.

Roentgenograms of the chest give reliable qualitative evidence of pulmonary hypertension in mitral stenosis, and numerous methods of estimating the degree of hypertension have been devised. By means of chest roentgenograms and pulmonary artery catheterization, correlations were obtained between 51 measurements of mean resting pulmonary arterial pressure and certain quantitative roentgenologic variables in 48 patients. With the use of statistical methods, several objective roentgeno-

logic parameters for the determination of pulmonary arterial pressure were investigated. Regression equations were derived which gave a strong correlation ($r=+0{\cdot}87$) between mean resting pulmonary arterial pressure and four roentgen parameters: the presence or absence of Kerley's B-lines, the height in millimeters of the pulmonary artery segment, the width in millimeters of the right descending pulmonary artery branch, and the " pulmonary arterial size " in centimeters.

Methods described by others for quantitation of pulmonary arterial pressure by roentgenologic measurements were found to have lower degrees of correlation when applied to the group of patients examined.—[Authors' summary.]

1072. **An Evaluation of Cardiovascular Contrast Media**
J. S. LEHMAN and J. N. DEBBAS. *Radiology* [*Radiology*] 76, 548–564, April, 1961. 5 figs., 39 refs.

The authors, working at the Hahnemann Medical College and Hospital, Philadelphia, have attempted to assess the relative merits of various contrast media commonly used in angiocardiography. They selected as the most useful criteria: (1) the viscosity of the solution because of the importance of rapid carriage of the medium to the site, often through a narrow catheter; (2) toxicity, as determined by studies on anaesthetized dogs and by the reactions of patients in routine clinical studies; (3) radiodensity, as determined by radiographs of known concentrations of the various solutions in a column of standard bore; and (4) the clarity of radiographs in angiocardiographic studies in dogs in which the various media were used. (Included in the materials assayed was " renovist ", a diatrizoate compound which is not yet commercially available.)

It was found that the most valuable attributes of a contrast medium were low viscosity, " hypaque sodium 50% " (sodium diatrizoate) having the lowest viscosity and " cardiografin 90% " (methylglucamine diatrizoate) the highest, and low toxicity, the diatrizoate compounds generally being the least toxic. Radiodensity appeared to confer less advantage in trial angiocardiographs both in animals and in clinical studies on patients.

The authors conclude that hypaque 75%, " ditriokon ", and renovist have the best radiographic qualities with the lowest incidence of reactions.

A. M. Rackow

1073. **The Roentgen Findings in *Pneumocystis carinii* Pneumonia**
S. B. FEINBERG, R. G. LESTER, and B. A. BURKE. *Radiology* [*Radiology*] 76, 594–600, April, 1961. 6 figs., 20 refs.

Pneumonia which is generally accepted as due to *Pneumocystis carinii* may occur in the premature or feeble full-term infant during the second to fifth months of life. Clinically, there are the usual features of pneumonia but without fever, and it is a characteristic of the condition that the respiratory embarrassment of the infant is disproportionate to the relatively slight physical signs.

Histologically, there is gross interstitial infiltration with mononuclear cells; the alveolar spaces are airless and filled with an exudate which stains characteristically with haematoxylin and eosin. Grossly, the lung retains its form and feels rubbery. Zones of pneumonia may be surrounded by zones of emphysema, the so-called " halo " emphysema as seen in the radiograph. The x-ray appearance is that of a diffuse nodular or granular shadowing which spreads throughout the lung fields and is particularly conspicuous at the periphery of the lung—a feature which may be diagnostic. Zones of density may alternate with areas of emphysema and when the lung becomes airless it is likely to show an atelectasis starting at the periphery.

The authors describe 2 cases seen at the University of Minnesota Hospitals, Minneapolis. Illustrative radiographs are reproduced [but they are not wholly adequate in quality to bring out the essential features].

A. M. Rackow

1074. **Valsalva's and Müller's Manœuvres and their Use in the Radiological Study of Some Pulmonary Conditions.** (Le manovre di Valsalva e di Müller e la loro utilità nello studio radiologico di alcune manifestazioni patologiche del torace)
G. DRAGONI and G. GALLI. *Radiologia medica* [*Radiol. med. (Torino)*] 47, 193–207, March [received June], 1961. 11 figs., 32 refs.

The authors consider the muscular changes that occur in the chest during Valsalva's and Müller's manœuvres and their effect on the x-ray findings. They suggest that because Valsalva's manœuvre increases pulmonary translucency and reduces pulmonary congestion it can be used as an aid to the diagnosis of certain parenchymal and hilar lesions. In their experience Valsalva's technique will enable parenchymal metastases to be demonstrated more clearly, especially if these are liable to be confused with vascular changes. Similarly, hilar adenopathies can be more easily differentiated from vascular shadows.

E. Giordani

1075. **The Value of Tomography in the Diagnosis of Bronchial Tumours.** (Die Bedeutung der Röntgenschichtuntersuchungen für die Erkennung von Bronchialtumoren)
A. GEBAUER. *Radiologe* [*Radiologe*] 1, 58–69, May, 1961. 31 figs., 25 refs.

In 80% of cases bronchial tumours arise from the greater bronchi and only in 20% from the small peripheral bronchi. It is important to be aware of such secondary processes as bronchiectasis, pneumonitis, or abscess which may be caused by the primary narrowing of the supplying bronchus. No case of radiological change of this type occurring above the age of 40 should be discharged before the possibility of a tumour has been finally excluded. For this purpose tomography is of the greatest help, is practically always conclusive, and is much to be preferred to bronchography, which should mainly be confirmatory. The optimum depth for visualizing the main bronchi in the antero-posterior view is 1 cm. dorsal to the half-way mark of the antero-posterior diameter. Supplementary cuts would be within centimetres of this depth both anteriorly and posteriorly. In

order to see the bronchus of the medial segment of the middle lobe, the superior bronchus of the lingula, the apical bronchi of both lower lobes, and the anterior segmental bronchi of both upper lobes lateral tomography is preferable. The optimum plane is 2 to 3 cm. less than the distance of the spinous processes, with further cuts extending a few centimetres downwards.

A direct search should be made for a narrowed bronchus, and it is surprising how large a tumour may exist without causing atelectasis; indeed, the tumour is as likely to cause localized emphysema. If the tumour grows submucosally it is rather more difficult to discover, but nevertheless a thickening of the wall should be noticeable and the outline is likely to be wavy. Sometimes a tumour extends into the lung tissue and forms a denser central shadow within the secondary atelectasis. Where a tumour arises peripherally the most important feature is that it is not just round, but shows various bulges which, however little marked, are quite diagnostic. Central cavities in tumours are frequent. The indirect signs of atelectasis should not escape detection wherever located; special attention should be paid to the accompanying localized emphysema in neighbouring areas. Special attention should be paid to the hilar shadows. If the hilum be large this is probably due to lymph-node involvement, but the hilar shadow may be smaller than normal owing to atelectasis and distortion of the pulmonary arteries. Bronchiectasis may be encountered in the nature of a secondary change. Sometimes a pneumomediastinum may decide whether the tumour has broken through the confines of the lung towards the mediastinum, in which case the tumour is inoperable. The main source of diagnostic error is the bronchus which suddenly changes its course and seems to be blocked. The other main source of error is misdiagnosis of the azygos vein above the right main bronchus as a tumour.

With increasing experience in tomographic interpretation the field for bronchography and bronchoscopy would appear to be narrowing considerably.

F. M. Abeles

1076. **Studies of Radioisotope-nephrography in Patients with Abdominal Tumours**

K. zum Winkel, K. E. Scheer, and I. Kazem. *British Journal of Radiology* [*Brit. J. Radiol.*] **34**, 241–245, April, 1961. 2 figs., 9 refs.

The vascularity and the secretory and excretory functions of each kidney may be studied by the external measurement of the γ radiation emanating from them after the intravenous injection of radioisotopically labelled contrast media. The measurement is made with a collimated scintillation detector placed over each kidney region; the pulses from the photo-multipliers in the detectors are recorded on multi-channel magnetic tape, which is played back at a faster rate and the resulting pulses fed into a ratemeter which is connected to a mechanical recorder. The count rate over the kidney shows an initial rise about 15 seconds after the intravenous injection of 0·3 μc. of isotope per kg. body weight contained in about 0·3 mg. of contrast medium per μc.; this is the vascular phase and is followed by a slower, more prolonged rise corresponding to the secretory phase; during the final excretory phase the count rate gradually falls. Decreased vascularity of the kidney will cause a lower rise during the vascular phase and thus a lower start to the secretory phase. In cases of reduced tubular secretion the rise in the secretory phase is less steep. Obstruction in the upper urinary tract causes diminution of the fall of the count rate in the excretory phase or prolongation of the rise in the secretory phase.

The authors, writing from the Czerny Hospital for Radiotherapy, University of Heidelberg, have used this method in investigating 138 patients with abdominal tumours (mostly neoplasms of the gastro-intestinal tract, bladder, and uterus and various types of abdominal metastasis). In 65% of cases the nephrographic pattern was abnormal, mainly in the excretory phase owing to obstruction of the upper urinary tract. In 104 cases the isotope nephrograms were compared with x-ray findings; in 88 cases the findings were similar, in 7 cases the nephrograms were considered to give wrong findings, and in 9 cases they gave pathological findings earlier than x-ray urography.

Many patients with abdominal tumours have renal complications, mainly obstruction and hydronephrosis, which are not evident clinically. Isotope nephrography is a valuable diagnostic aid in these patients; the function of each kidney may be assessed separately, the amount of contrast medium used is so small that the technique may be used for uraemic patients, and the examination may be repeated as often as is necessary as the radiation dose is only about 1% of that received during x-ray urography.

Michael C. Winter

1077. **Renal Artery Stenosis**

D. Sutton, F. J. Brunton, and F. Starer. *Clinical Radiology* [*Clin. Radiol.*] **12**, 80–90, April, 1961. 17 figs., 10 refs.

Stenosis of the renal artery was diagnosed by arteriography in 46 patients (including 37 with hypertension) at St. Mary's Hospital, London, three different techniques being used—translumbar aortography, percutaneous transfemoral catheterization, and percutaneous selective renal arteriography. The hazards of these investigations are discussed, the authors stating that most accidents have been due to excessive doses of contrast medium. They consider that 70% " diaginol " (sodium acetrizoate) is potentially dangerous; for free injections into the aortic lumen they give a maximum dose of 20 ml. of 76% " urografin " (sodium diatrizoate).

The stenosis shown was usually a smooth narrowing of the lumen less than 1 cm. in length, nearly always at or near the origin of the renal artery, and unilateral in all except 4 patients. Some of the patients were being examined for vascular disease, not hypertension, renal artery stenosis being a chance finding in 20. Of these 20, 11 also had hypertension, but 5 had normal blood pressure.

The importance of preliminary intravenous pyelography is stressed, the characteristic features being a smaller smooth kidney which concentrates well and often appears spastic. This spastic appearance is frequently

seen with simple dehydration and can be eliminated by deliberately giving the patient a drink before the examination. This "water-load test" was carried out on 4 patients, all of whom were given 500 ml. of water before a second pyelogram was taken. On the normal side the calyces filled out with dilute contrast material while on the side of the stenosis the shadow was still dense and spastic. *D. E. Fletcher*

1078. **Cystography in Bladder Tumours. A Technique Using "Steripaque" and Carbon Dioxide**
F. H. DOYLE. *British Journal of Radiology* [*Brit. J. Radiol.*] **34**, 205–215, April, 1961. 8 figs., 14 refs.

At Hammersmith Hospital, London, double-contrast cystography was carried out on 50 occasions in patients with tumour of the bladder. The contrast medium used was "steripaque" (a sterile suspension of barium sulphate in water), 150 ml. of which was introduced into the empty bladder. After screening and radiographs had been obtained of the filled bladder most of the steripaque was withdrawn, leaving a residue of 20 to 30 ml.; 150 to 200 ml. of carbon dioxide was then introduced. The finely particulate barium adhered to the tumour surface and the carbon dioxide provided double contrast.

The author considers that the technique has a place in the diagnosis and assessment of bladder tumours, particularly when cystoscopy is difficult or impossible. In one case it failed to show a small sessile tumour in the trigone which had been irradiated, but otherwise it proved diagnostically reliable. Comparison of retrograde cystograms with excretion cystograms showed that the latter were sometimes unreliable, failing on occasion to demonstrate even a large tumour. In addition to demonstrating the site and size of the tumour cystography may supply other information in some cases; for instance, it is possible that the breadth of the tumour base may help in the assessment of malignancy and the rigidity, fixation, and displacement of the bladder wall may indicate infiltration into the bladder musculature and beyond. *Michael C. Winter*

1079. **Transient Proteinuria following Intravascular Injection of Contrast Media**
J. A. KIRKLAND and M. R. HASLOCK. *Lancet* [*Lancet*] **1**, 693–695, April 1, 1961. 4 figs., 17 refs.

Slight degrees of renal damage following intravascular injection of contrast medium for aortography and intravenous pyelography have been little mentioned in the literature, although more serious complications have often been described. The authors of this paper from the University of St. Andrews and the Royal Infirmary, Dundee, have investigated the incidence of proteinuria following these procedures.

Samples of urine taken before and after injection of contrast medium were tested for protein with the paper strips "albustix" and "uristix", and the results confirmed by dialysis and subsequent electrophoresis. It is stated that the strip tests do not give false positive results when radio-opaque medium is present in the urine. A total of 53 patients subjected to intravenous pyelography were studied. Of 37 who had no proteinuria before the examination, 7 developed it afterwards; proteinuria was present in 16 patients before examination and in 2 of these the results of the protein tests became more positive after it. Aortography was carried out on 14 patients; proteinuria developed after the examination in 3 out of 10 who had no proteinuria before aortography, while in 2 out of 4 with proteinuria originally the results of the tests became more positive after the examination.

The authors recommend carrying out paper strip tests before and after these examinations so that any renal side-effects may be detected early. *Michael C. Winter*

RADIOTHERAPY

1080. **Value of Radiation Therapy in the Management of Intracranial Metastases**
F. C. H. CHU and B. B. HILARIS. *Cancer* [*Cancer (Philad.)*] **14**, 577–581, May–June, 1961. 2 figs., 2 refs.

From January, 1954, to June, 1958, 218 patients with intracranial metastases were referred for radiation therapy at the Memorial Hospital, New York, and the results in these cases are reported. All 218 patients received some radiotherapy. The primary lesion was carcinoma of the breast in 85 cases and carcinoma of the bronchus in 74 cases, but primary sites in most parts of the body were represented. In almost every case the presence of intracranial secondary deposits was confirmed by a neurologist and many patients were in coma or had Jacksonian seizures at the time of irradiation. The irradiation given was 250-kV. x rays at an H.V.L. of 2·0 mm. Cu through two opposing lateral fields to irradiate the whole brain above a line drawn from the superior orbital ridge to the external auditory meatus. The eyes were shielded. The aim was usually to give 3,000 rads in 3 weeks, but the average dose was 1,500 to 2,000 rads in 2 weeks. Increased intracranial pressure was recognized as a serious complication and treatment was started with daily doses of approximately 50 rads, increasing to 300 rads a day. The dosage given was varied with the patient's response, and some patients received chemotherapy or hormone therapy in addition to radiotherapy.

Of the 218 patients in the series, 35 did not complete the course of treatment and 12 were lost to follow-up; of the remaining 158 patients, who completed the intended treatment, 77·8% had a favourable response. The average duration of the remission was 4·7 months and the average survival was 6·6 months. In 17 cases the patient received a second course of therapy and 12 of these responded. Three patients received a third course and there was evidence of brain damage in only one case.

The authors feel that this is a useful method of palliation not only for the patient, but also in easing the burden of their care. They stress the need for both early diagnosis and of irradiating the whole brain and have gained the impression that 2 to 3 times as many patients failed to respond to therapy with a dose of 2,750 rads or less as with a larger dose, but point out that this may have been due to selection. *E. D. Jones*

1081. **A New Drug in the Treatment of Leucopenia Due to Irradiation for Malignant Disease.** (Sull'impiego di un nuovo farmaco nelle leucopenie degli irradiati per forme neoplastiche)
G. Conte and S. Casara. *Minerva medica* [*Minerva med. (Torino)*] **52**, 1640–1644, May 5, 1961. 41 refs.

This is a report from the Civil Hospital, Padua, on the use in radiotherapy of a new anti-anaemic and anti-leucopenic agent composed of sodium thioporpanoate, benzimidazyl-1-betapyridyl-carbonamide-2-propanoic acid, and sodium cobaltithiopropanoate. Thiopropanoate contains the SH radical which enhances synthesis of deoxyribonucleic acid; the benzimidazyl fraction has a structural resemblance to a degradation product of vitamin B_{12} (cyanocobalamin), and the cobalt fraction catalyses the fixation of iron in haemoglobin. The drug was given both for treatment of leucopenia after onset and also as a prophylactic, usually parenterally, but sometimes orally if parenteral treatment was inadvisable or as a maintenance supplement.

A detailed list is given of 32 cases treated either by x rays or cobalt beam, including both tumour and integral doses; the latter is far the better indicator of radiation effects. In 15 cases (46·9%) the leucocyte count was increased by the drug and in 12 (37·5%) a fall in the count was arrested—that is, a positive result was obtained in 84·3% of cases. In 5 cases (15·6%) there was no effect on a progressive fall, but these cases were mostly advanced, with bony metastases. The higher the integral radiation dose, the less likely was benefit to be obtained from the drug. It was well tolerated, with only one case of intolerance (cutaneous allergy); it also had a tonic effect, increasing the appetite and sense of well-being.
J. Walter

1082. **Intravascular Irradiation of the Internal Mammary Lymph Nodes in Breast Cancer**
R. D. Brasfield and U. K. Henschke. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **85**, 849–859, May, 1961. 4 figs., 10 refs.

Writing from the Memorial Center for Cancer and Allied Diseases, New York, the authors review the available statistics from various sources for cases of cancer of the breast with deposits in the internal mammary lymph nodes. It appears that 34% of patients with metastases to these nodes survive 5 years after surgical resection of the internal mammary chain. This resection produces a higher postoperative morbidity and the alternative and more widely used treatment is post-operative x-ray therapy. In their opinion the latter treatment has the disadvantage of causing skin and lung changes and necessitates 3 to 5 weeks' additional treatment time. They therefore describe in detail the treatment of these nodes by the insertion of a radioactive source into the internal mammary artery.

Necropsies showed that 87% of all internal mammary lymph nodes lie within 1·0 cm. of the artery and 97% within 1·5 cm. At the time of the operation the internal mammary artery is ligated and an empty nylon tube inserted into it. After the patient has left the operating theatre the radioactive wire is introduced into the nylon tube and left in position for 5 to 8 days until the desired dose has been delivered. The wire used is 15 cm. long with a total activity of 15 mg. radium equivalent (=10 mc. ^{60}Co or 22·5 mc. ^{192}Ir). Details of the technique are given. Since January, 1957, 50 patients have been treated by this method, without early or late complications. As yet the series is too small to enable the results of this method to be compared with those of surgical resection or x-ray therapy.
M. P. Cole

1083. **Treatment of Locally Advanced Carcinoma of the Breast with Roentgen Therapy and Simple Mastectomy**
H. L. Atkins and W. D. Horrigan. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **85**, 860–864, May, 1961. 7 refs.

At the Presbyterian Hospital, New York, a high proportion of patients with carcinoma of the breast are deemed unsuitable for radical mastectomy. Very strict criteria of operability are observed and also biopsy of the highest axillary and internal mammary lymph nodes must show no invasion by tumour. The authors report the results of radiotherapy after 3 and 5 years in 79 patients with inoperable breast carcinoma and examine whether or not irradiation controls the local disease. Simple mastectomy to facilitate x-ray therapy was not considered possible in some cases, in which radiotherapy alone was given. The technique of therapy was that of McWhirter, using opposing tangential fields to the breast area. The supraclavicular and axillary regions were included in opposing antero-posterior fields. At first, with 250-kV. radiation and a H.V.L. of 1·5 mm. Cu a skin dose of 4,250 r. was delivered in 3 or 4 weeks. Later a 22·5-MeV. betatron was used to treat a number of patients, the technique being the same except that a single anterior field covered the supraclavicular region. A dose of 5,000 r. was given in 4 weeks.

Of 43 patients who have been followed up for 5 years, 9 have survived. In 3 patients in this group the condition was inoperable for medical reasons and these 3 include 2 who survived 5 years. If these cases are excluded the survival rate is 17·5% (7 out of 40). A marked difference in survival was observed between those patients treated by simple mastectomy and radiotherapy (3 out of 28) and those who had radiotherapy alone (4 out of 12). The local recurrence rate was assessed in patients surviving 3 years or more. Of the 12 patients treated by mastectomy and radiation, only 2 (16·7%) had residual or recurrent tumour compared with 34 (87%) of 39 patients who had radiotherapy alone. Complications, mainly pneumonitis and subsequent fibrosis, were not troublesome, but were almost 7 times more frequent in patients having simple mastectomy. This is unexplained. It is pointed out, however, that the two groups were not strictly comparable.

The authors state that many breast tumours which have shown a good initial response to irradiation recur later. Full x-ray therapy alone does not control the primary tumour in the majority of cases. It is suggested that simple mastectomy performed on suitable patients might improve the survival rate and certainly decrease the problems of local disease.
W. Duncan